# SILVER MEDIATED FUNCTIONALIZATION OF [3.2.1]BICYCLIC SYSTEMS OBTAINED FROM TETRAHALOCYCLOPROPENES

By

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"In trying to understand the mystery of life, man has followed many different approaches. Among them there are the ways of the scientist and mystic, but there are many more; the ways of the poets, children, clowns, shamans, to name a few. These ways have resulted in different descriptions of the world, both verbal and non-verbal, which emphasize different aspects. All are valid and useful in the context they arose. All of them, however, are only descriptions, or representations, of reality and are therefore limited. None can give a complete picture of the world."

The Tao of Physics, Fritjof Capra

This work is dedicated to all my teachers who have educated me

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Abstract of Dissertation Presented to the Graduate School
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Major Department: Chemistry

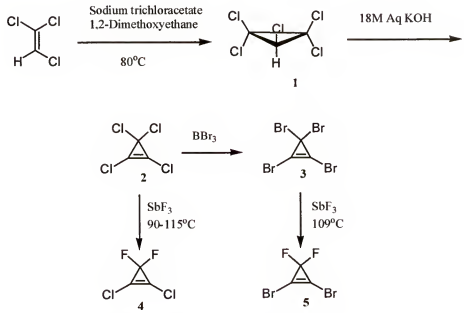
The tetrahalobicyclo[3.2.1]octa-2,6-dienes are obtained by the Diels Alder reaction of furan and cyclopentadiene with tetrabromo or tetrachlorocyclopropene. These oxabicyclic and carbocyclic systems are versatile synthetic intermediates that are analogous to the compounds obtained from [4+3] oxyallyl addition to furan or cyclopentadiene. Treating these compounds with cationic silver affords the perhalogenated oxabicyclic cation that can be efficiently trapped by electron rich aromatic systems. Further investigations with regards to the reactivity of these cations were studied and the generality of this silver promoted arylation was explored. Reaction of these cations with water produces the corresponding dihaloenones. The bicyclic ketones that are thus obtained are versatile synthons in that they can be treated with various nucleophiles to afford highly substituted bicyclic compounds in good yields. Addition of Grignard reagents gives solely the 1,2 addition products in high yields while the addition of cuprates gives 1,4 addition products. Palladium catalyzed Suzuki

couplings of these dibromoenones have also been investigated and found to undergo Suzuki couplings specifically at the beta position forming the product in very high yields thus making these oxabicyclic systems very useful synthons. The intramolecular cationic cyclizations have also been studied. During the course of these investigations the reaction between 2,5-dimethyl furan and tetrabromocyclopropene afforded the primary unrearranged adduct. This compound was used to study the rates of rearrangement, in various solvents, by NMR and the implications of these results to the mechanism of rearrangement have been discussed.

CHAPTER 1
CHEMISTRY OF HALOGENATED CYCLOPROPENES

**Introduction**

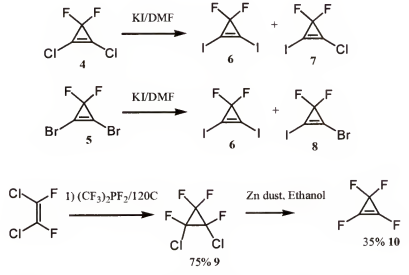
The synthesis of halogenated cyclopropanes and cyclopropenes was first reported in a series of papers by Tobey and West.[1a-d] These authors showed that the thermal decarboxylation of sodium trichloroacetate in dimethoxyethane produces dichlorocarbene, which reacts with trichloroethylene to afford pentachlorocyclopropane (**1**). Pentachlorocyclopropane was subsequently converted to tetrachlorocyclopropene (**2**) by treatment with aqueous potassium hydroxide.




Scheme 1.1. Synthesis of Halogenated cyclopropenes

Tetrachlorocyclopropene was readily converted to tetrabromocyclopropene (**3**) by treatment with stoichiometric amounts of boron tribromide. These halogenated

cyclopropenes, **2** and **3**, were respectively converted to 1,2-dichloro-3, 3-difluorocyclopropene (**4**) and 1,2-dibromo-3, 3-difluorocyclopropene (**5**) by treatment with $SbF_3$ (Scheme1.1). The formation of the various halogenated cyclopropenes, **3**, **4** and **5**, were explained on the formation of the corresponding cyclopropenium cation that undergoes halogen substitution. The 1,2-dichloro-3, 3-difluorocyclopropene (**4**) and 1,2-dibromo-3, 3-difluorocyclopropene (**5**) have been converted to the mono and diiodo cyclopropenes respectively using potassium iodide in DMF.[2a]




Scheme 1.2 .Synthesis of mono, diiodocyclopropenes, and tetrafluorocyclopropenes.

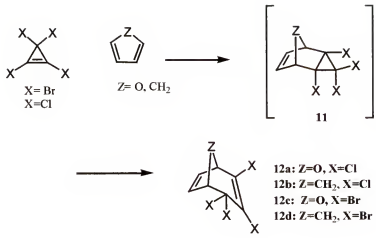
Tetrafluorocyclopropene was first synthesized by Camaggi et al.[2b] The synthesis involved the reaction of difluorocarbene and 1,2-dichlorodifluoroethylene to produce 1,2-dichlorotetrafluorocyclopropane (**9**). Reductive dechlorination of this cyclopropane with zinc dust afforded tetrafluorocyclopropene (**10**). The tetrafluorocyclopropene was found to have similar reactions as other halogenated cyclopropenes.

Tetraiodocyclopropene has been reported by Weiss et al.[2c] The compound was synthesized by treating tetrachlorocyclopropene with trimethylsilyliodide at 0°C or boron

triiodide at –78°C in very good yields. Tetraiodocyclopropene was found to be explosive. The halogenated cyclopropenes are versatile compounds that have remarkable reactivity. Various research groups have studied their reactivity. These reactions can be categorized as follows.

**Cycloaddition Reactions of Tetrahalocyclopropenes**

The various cycloadditon reactions of tetrahalocyclopropenes can be further classified into various categories. The Diels Alder reaction is the most studied reaction in cyclopropene chemistry. This reaction is of synthetic importance because of the introduction of a three-carbon fragment into the ends of a dienophile. The overall reaction involves an initial [4+2] addition of the cyclopropene to afford the primary adduct. The primary adduct can then undergo a disrotatory rearrangement to afford the corresponding [3.2.1] bicyclic systems, the driving force for the reaction is the relief of ring strain associated with the fused cyclopropane. The ability of tetrahalocyclopropenes to take part in Diels-Alder reaction was first reported in a series of seminal papers by Tobey and Law.[3a-c] Prior to this report, it was well known that the parent hydrocarbon cyclopropene does undergo Diels-Alder reaction with cyclopentadiene. 3-methyl cyclopropene reacts with cyclopentadiene to afford the endo product in low yield and that the 3,3-disubstituted cyclopropenes fail to undergo the same reaction.[4a-e] The overall chemical transformations that occur when tetrahalocyclopropenes react with furans are shown in Scheme 1.3. Tobey and Law[3a] also determined by competition experiments that the tetrahalocyclopropenes are less reactive compared to cyclopropene, and that tetrabromocyclopropene is more reactive than tetrachlorocyclopropene and that 3,3-difluoro cyclopropenes are slower reactants than tetrabromo and tetrachloro-cyclopropene.



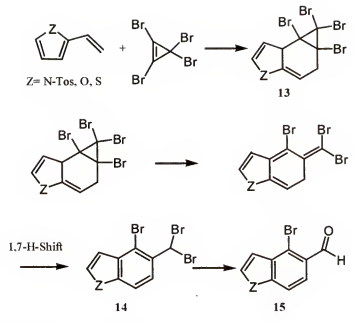

Scheme 1.3. General Diels Alder reaction of tetrahalocyclopropenes.

Stable intermediates (**11**) from the Diels-Alder reaction were obtained when the reaction involved 1,2,3-trichloro-3-fluorocyclopropene, 1,2-dichloro-3,3-difluoro-cyclopropene, or 1,2-dichloro-3,3-difluorocyclopropene as dienophiles. The Diels-Alder adducts obtained from the reaction of 1,3-butadiene and halogenated cyclopropenes did not under go rearrangement. The stereochemistry of the initial adduct (**11**) was originally assumed as being *endo*. Subsequent work by Apeloig et al.,[5a] Müller et al.[6a, b] and Battiste and Posey[7] showed that the primary adducts obtained possess *exo* stereochemistry. Investigations by Apeloig et al. of the reaction between tetrachlorocyclopropene[5b] and substituted butadienes showed that the adduction was *exo*. In addition, it was observed that changing the geminal chlorines at the three position of the cyclopropene to hydrogen gave a mixture of *endo* and *exo* adducts, the former being the major product. Based on the experimental evidence and calculations it was concluded that sterics favor the *exo* adduction and that the intrinsic electronics favor endo adduction. The *exo* stereoselectivity of these reactions gained further acceptance when Müller's lab showed that the addition of 1,2 dichloro-3,3-difluorocyclopropene to 1,4-diphenyl1,3-

butadiene and 1,3 diphenyl isobenzofuran gives *exo* adducts. The 3,3-difluorocyclopropenes in particular were attractive starting materials as the adducts obtained from these compounds do not undergo subsequent rearrangement and therefore preserve the stereochemical information of the Diels-Alder reaction. Battiste and Posey[6c] investigated the reactions of 3,3-difluoro-cyclopropenes with furan, cyclopentadiene, and related systems. In all the cases that were investigated the obtained adducts were found to be *exo*. Several papers[7a-c] that deal with theoretical calculations that tend to explain the stereochemistry of these reactions, particularly that of cyclopropene, have been published. Most of these papers deal with trying to understand the importance of secondary orbital interactions.

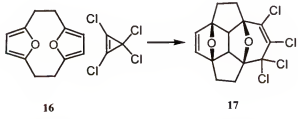
The variety of products that can be obtained from the Diels-Alder reaction depends not only on the cyclopropene used but also on the diene. Several dienes other than furan and cyclopentadiene have been explored in this reaction. Sietz et al. [8a,b] showed that the Diels-Alder reaction of tetrabromocyclopropene and tetrachloro-cyclopropene with 2-vinylhetarenes proceeds smoothly. The primary adduct thus formed undergoes selective bond cleavage and affords the corresponding indoles, benzofurans and benzothiophenes (**14**) in good yields.

The geminal dibromides were then converted to the corresponding aldehydes (**15**) by treatment with alcoholic potassium hydroxide. It is interesting to note that even though the Diels-Alder reaction can potentially occur either with the furan as the diene or with one of the double bonds from furan and the vinyl double bond acting as the diene. The products that are obtained are exclusively formed by the reaction of the cyclopropene with the vinyl double bond participating as the reacting diene.



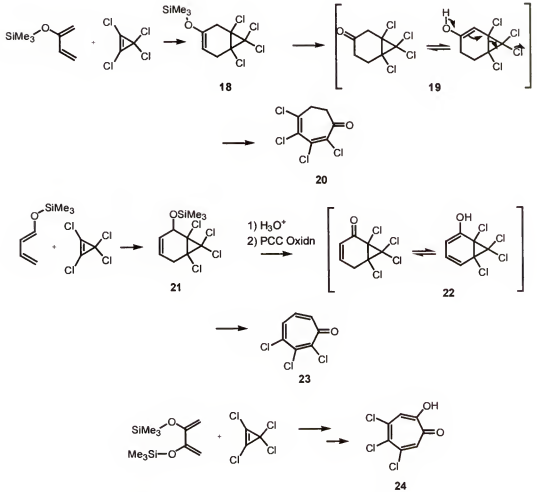

Scheme1.4. Diels-Alder reaction with vinyl heterocycles.

Battiste et al.[8c] had reported an unusual reaction between [2,2](2,5)-furanophane (**16**) with tetrachlorocyclopropene. The product was identified as 5,6,7,7-tetrachloro-16,17-syn-dioxahexacyclo[9, 2, 2, 1, $1^{4,8}$, $0^{4,14}$, $0^{8,15}$]-heptadec-5,12-diene (**17**) by X-ray diffraction. This is an unusual reaction in that the product obtained from the Diels Alder reaction between tetrachlorocyclopropene and the furanophane undergoes an intramolecular Diels-Alder reaction to afford the final product (Scheme 1.5).




Scheme 1.5. Diels Alder reaction of tetrachlorocyclopropene and furanophane

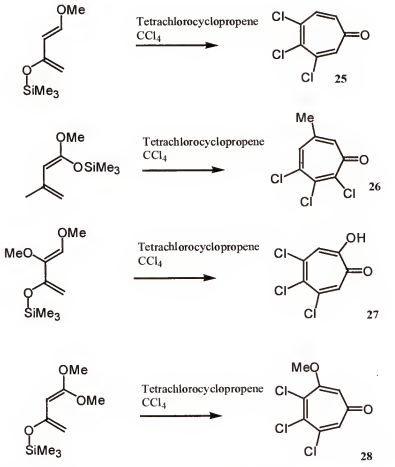
Sietz et al.[9] investigated the reaction of tetrachlorocyclopropene with 1,3 butadiene that had electron donor (trimethylsilyloxy) groups and obtained the corresponding bicyclo[4.1.0]heptenes.




Scheme 1.6. Sietz's synthesis of tropones and tropolones

These compounds were subjected to acid hydrolysis and oxidation to yield a variety of chloro-substituted derivatives of tropone. The formation of tropone was explained by the vinyl cyclopropane rearrangement of the enol tautomers **19** and **22** that are obtained as intermediates. The substitution pattern of the chlorines depends on the type of diene that was used in the reaction (Scheme 1.6).

Banwell et al.[10a] reported a one pot synthesis of tropones and tropolones by the Diels-Alder reaction of tetrachlorocyclopropene with various trimethylsiloxybuta-1,3-dienes. These authors were able to show that the Diels-Alder reaction followed by ring expansion-dehydrochlorination process all happen in a single operation to afford tropones and tropolones. The different dienes that were subjected to this chemistry are shown in Scheme 1.7. The yields of the desired products were about 74-30%.

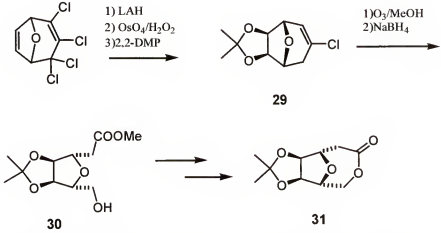



Scheme 1.7.Banwell's synthesis of tropones and tropolones.

These investigators also found that diphenylcyclopropenone does not react with Danishefsky's diene to afford the corresponding tropones. Similar chemistry involving butadienes has been reported by Breslow.[10b] 2,3,4,4-Tetrachloro-8-oxa-

bicyclo[3.2.1octa-2,6-diene (**12b**) has been used by the Gensler lab as starting material for the synthesis of C-Nucleosides.[10c, d]

This is perhaps the only reported use of this compound towards the synthesis of a natural product or a related substance. The overall synthetic transformation involved the reductive dechlorination of **12b** using lithium aluminum hydride to afford the 3-chloro-8-oxa-bicyclo [3.2.1]octa-2,6-diene (**29**). The monochloro compound was then subjected to dihydroxylation using osmium tetroxide and hydrogen peroxide. The reaction occurred regiospecifically as well as stereospecifically to afford the *exo cis* dihydroxy compound that was readily converted to the isopropylidene (**30**) derivate with2,2-dimethoxypropane.



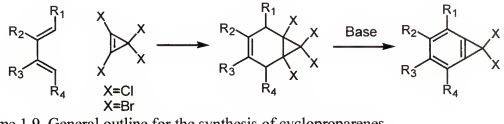

Scheme 1.8. Gensler's synthesis of carbohydrates from tetrachloroxabicyclic systems.

Ozonolysis of the resulting compound in methanol as solvent followed by borohydride reduction affords the methyl ester. The methyl ester was converted to the lactone (**31**) under standard conditions (Scheme **1.8**). The lactone (**31**) served as the main intermediate towards the synthesis of C-nucleosides. The principle limitation of this methodology towards making nucleosides is the formation of racemic products.

**Synthesis of Cycloproparenes using Halogenated Cyclopropenes**

Cycloproparenes[11a-c] are a class of compounds that have a cyclopropane ring fused on to an aromatic ring. These compounds continue to be of great interest to physical organic chemists, as they possess a highly strained carbon skeleton and are considered good candidates to study resonance and chemical bonding in strained systems. The strain energy of cyclopropa benzene was measure by Billups[11d] and found to be about 68 kcal $mol^{-1}$. The cations, anions and radicals obtained from these systems have unique properties as they are resonance stabilized by the aromatic system and are destabilized by highly strained cyclopropane ring. These compounds are highly reactive and most of the reactions involve the cleavage of the cyclopropane ring.

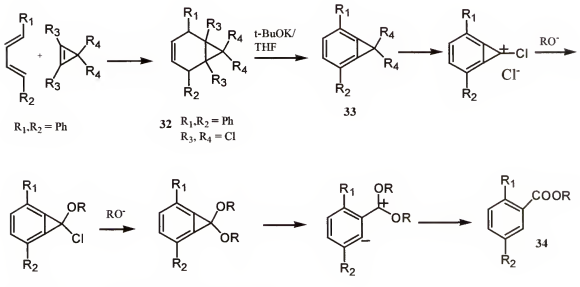
Several methods have been reported towards the synthesis of cycloproparenes. The synthetic routes that exclusively involve the use of tetrahalocyclopropenes will be mentioned in this section. A recent review by Halton covers the various methods that have been used to synthesis these compounds.[11a] Scheme 1.9 illustrates the general synthesis of cycloproparenes. Cyclopropabenzene and several other cyclopropaarenes have been synthesized using the Diels-Alder reaction of halogenated cyclopropenes and *trans trans* butadienes.[12a]




Scheme 1.9. General outline for the synthesis of cycloproparenes

Halton et al.[12a] synthesized 1,6,7,7-tetrahalogenobicyclo[4.1.0]hept-3-enes (**32**) in moderated yields. Dehydrohalogenation of **32** with Potassium t-butoxide afforded the

cyclopropabenzene (**33**) in quantitative yields. When other tetrahalogeno-bicyclo[4.1.0]hept-3-enes, obtained from tetrabromo and tetrachlorocyclopropene, were subjected to dehydrohalogenation the corresponding cyclopropabenzenes were not isolable.

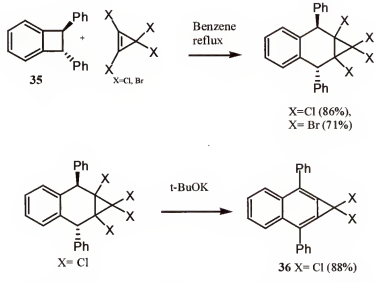



Scheme 1.10. Reactions of cycloproparenes

Instead, the t-butyl esters of 2-alkyl-5-alkyl benzoic acids were isolated in low yields. The authors were able to convert the isolated cyclopropabenzene (**33**) into methyl 2,5-diphenyl benzoate by treating it with methanolic KOH, thus concluding that the formation of the esters (**34** and orthoesters in certain cases) can be explained by considering the respective cyclopropabenzenes as possible intermediates. The possible pathway suggested for the formation of these esters is shown in Scheme 1.10. Glück et al.[12b] were able to synthesize the difluorocyclopropabenzene using similar chemistry. The diflurocyclopropabenzene thus obtained was found to be stable and isolable. It has been noted by Halton et al., Glück et al. and Müller et al. that the Difluorocyclo-

proparenes are more stable and isolable compared to the corresponding dichloro and dibromo analogs.

Halton et al.[12c-e] were able to synthesize 1,1-dichlorocyclopropa[b]naphthalene in a similar fashion (Scheme 1.11).

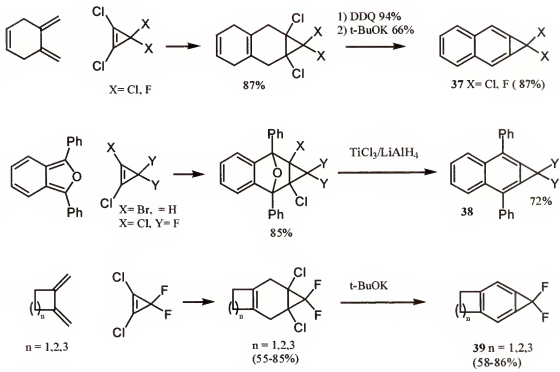



Scheme1.11. Halton's synthesis of 1,1-dichlorocyclopropa [b]naphthalenes

However, the corresponding dibromo analog could not be synthesized through similar reactions. Similar chemistry was exploited by Müller et al.[12a, b] towards the synthesis of 1,1-difluoro- naphtho[b]cyclopropenes. 1,1-dichlorocyclopropa-[b]naphthalenes and 1,1-difluorocyclopropabenezenes.

Müller et al.[12a-c] were also able to synthesize cyclopropabenzenes from the Diels-Alder products of halogenocyclopropenes and furans and isobenzofurans. The overall synthetic scheme followed by Müller's group is shown in Scheme 1.12. Similar chemistry was exploited towards the synthesis of cyclopropa[f]indenes[12d-f] and heterocyclic cyclopropa[f]indenes.[12g-i]. In most cases 1,2-dichloro-3,3-difluorofluorocyclopropene was the reagent of choice. In conclusion, it can be said that

tetrachlorocyclopropene is a useful reagent towards the synthesis of various cycloproparenes.



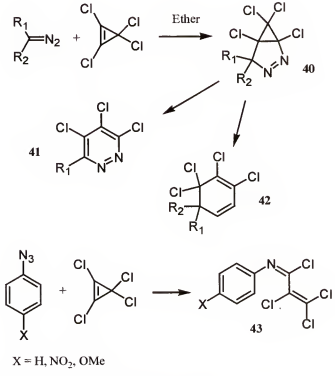

Scheme 1.12. Müller's synthesis of cyclopropa-arenes.

**Halogenated Cyclopropenes in 1,3-Dipolar Reactions**

Tetrahalocyclopropenes are known to be good dienophiles in Diels-Alder reactions. This reaction has been successfully studied and used towards several unique compounds. However, the ability of these cyclopropenes to react as 1,3-dipolarophiles has not been studied thoroughly. The chemical literature has a few papers that point to the more general nature of this reaction. Thus, 1,3-Dipolar reactions of tetrahalocyclopropenes is an area that is yet to studied and used in synthesis.

The 1,3-dipolar additions of tetrachlorocyclopropene with substituted diazomethanes and aryl azides were first reported by Dehmlow[14a] in a short

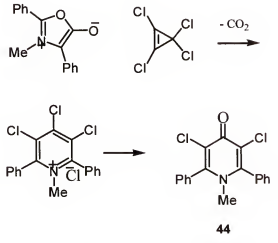
communication. In the case of diazomethanes, bicyclic compounds were obtained as the primary products.




Scheme 1.13. 1,3-Dipolar reactions of tetrachlorocyclopropene

The reaction of diazomethane with tetrachlorocyclopropene was also reported independently by Cohen.[14b] The primary products obtained by addition of diazomethane and monosubstituted diazomethane rearrange with loss of HCl to afford the pyridazines while the primary adducts obtained from disubstituted diazomethanes afforded the dihydropyridazines. The aryl azides were also found to react with tetrachlorocyclopropene to afford the corresponding 2,3,3-trichloro-N-phenyl-acrylimidoyl chlorides (Scheme 1.13). Dehmlow[14c] also reported the reaction of tetrachlorocyclopropene with sodium azide where the ring-opening product was obtained. Gompper[15] reported the reaction of tetrachloro- and tetrabromocyclopropene with

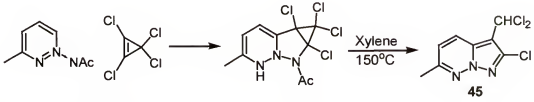
trimethylsilylazide to afford the corresponding 4,5,6-trihalo-triazines in 40-50% yields. The 1,3-dipolar cycloaddition of tetrachlorocyclopropene with 3-Methyl-2, 4-diphenyl-1,3-oxazolium-5-olate has been reported by Deem.[16] The resulting 4-chloropyridinium salt underwent hydrolysis under mild conditions to form the pyridinone (**44**) (Scheme 1.14).




**44**

Scheme 1.14. Deem's synthesis of pyridinones

Osawa et al.[17] investigated the reaction of tetrachlorocyclopropene and 1,2-dibromo-3,3-difluorocyclopropene with pyridazinium ylides. The products from these reactions were identified as cyclopropapyrazolo-pyridazines.




**45**

Scheme 1.15. 1,3-Dipolar reactions with pyrazolopyridazines

Thermolysis of these products gave the corresponding pyrazolopyridazines(**45**) (Scheme 1.15). The yields for these cycloaddition reactions were low (37-19%). The

1,3-dipolar cycloaddition reactions of halogenated cyclopropenes can be therefore regarded as a field that is yet to be explored and studied thoroughly.

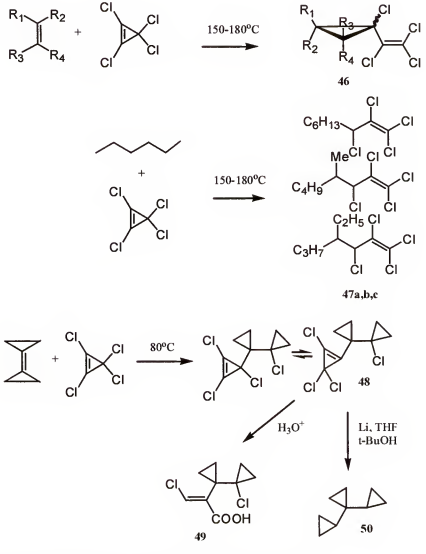
**Thermal Rearrangements of Tetrahalocyclopropenes**

Tetrachlorocyclopropene upon being heated to 180°C undergoes thermal rearrangement to afford tetrachlorovinyl carbene. The resulting carbene intermediate has been used towards the synthesis of cyclopropanes. Billups et al.[18] have reported that flash vacuum pyrolysis of several halogenated cyclopropenes leads to the formation of the corresponding allenes. The mechanism suggested is the formation of the trichloro-vinyl carbene intermediates that undergo a 1,2 halogen shift to afford the allenes.

The reactivity and synthetic utility of the trichlorovinyl carbene generated from tetrachloro-cyclopropene has been studied extensively by the de Meijere group.[19a] It was found that normal olefins and acrylates are attacked by tetrachlorocyclopropene, via the carbene intermediate, at 150-180°C to afford the corresponding cyclopropanes (**46**) in good yields. The resulting cyclopropanes retain the stereochemical information possessed by the olefins (Scheme **1.16**).

The formation of the intermediate trichlorovinyl carbene was furthered when it was found that tetrachlorocyclopropene forms C-H insertion products when heated in the presence of saturated hydrocarbons. Thus, reaction of tetrachlorocyclopropene with n-hexanes at 180°C gives isomeric tetrachloroolefins.[19b] The reaction of tetrachlorocyclopropene with 1,1'-Bicyclopropylidene proceeds at 80°C to afford12,3-trichloro-3-[1-(1-chlorocyclopropyl)-cyclopropyl]cyclopropene (**48**).[20] The product is supposed to be formed in an $S_N2'$ fashion where the highly reactive 1,1'-Bicyclopropylidene acts as a nucleophile. The product (**48**) is unstable and undergoes

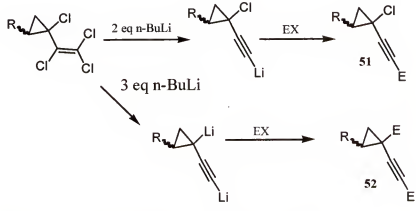
hydrolysis to afford (E)-3-chloro-2-[1-(1-chlorocyclopropyl)cyclopropyl]-acrylic acid(**49**) (Scheme 1.16).




Scheme 1.16. Thermal reactions of tetrachlorocyclopropene

Compound (**48**) was converted to the parent hydrocarbon 1,1`-dicyclopropylcyclopropane (**50**) by reductive dechlorination. The adducts obtained by the reaction of tetrachlorovinyl carbene and ethylene and propylene have been used as $C_5$ building blocks.[21a,b] These compounds upon being treated with 2 equivalents of n-BuLi

afforded the corresponding Lithium acetalydes that could then be trapped by various electrophiles to afford the substituted cyclopropylacetylenes (**51**). Similar reaction with 3 equivalents of n-BuLi afforded the dianions that could then be trapped with 2 equivalents of electrophiles to afford difunctional cyclopropyl acetylenes (**52**) in very good yields (Scheme 1.17).

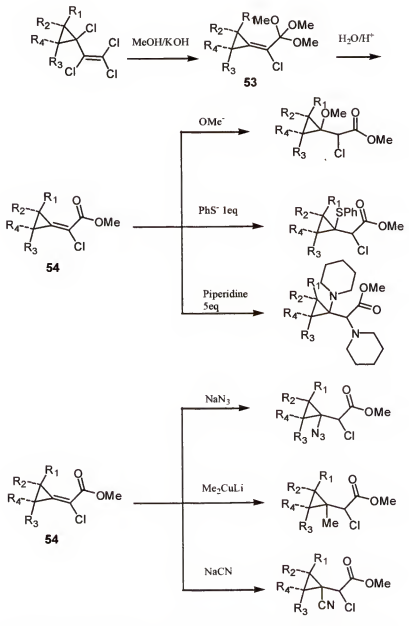



Scheme 1.17. Reactions of 1-trichlorovinyl-1-chloro cyclopropanes

The acetylenes thus obtained were found to be good dienophiles and reacted with several dienes to afford the Diels-Alder products. Treatment of 1-chloro-1-(trichlorovinyl) cyclopropane (having various alkyl substituents on the cyclopropane) with methanolic potassium hydroxide exclusively afforded orthoesters (**53**) of the corresponding methylenecyclopropane . This is rather remarkable as the starting compound could have undergone several reactions viz., displacement of the 1-chloro group to form a cyclopropyl cation that could either be captured by a nucleophile or undergo ring opening. The products were formed by $S_N2'$ displacement of the 1-chloro followed by two subsequent $S_N2$ displacements.

The orthoesters were converted to their corresponding methylenecyclopropane esters (**54**) in a facile manner. The esters thus obtained are very reactive Michael

acceptors and react readily with nucleophiles such as sodium thiophenolate, secondary amines, azide, cyanide and lithium dimethylcuprate (Scheme 1.18).[22a]




Scheme 1.18. Michael type reactions with methylene cyclopropane esters

The Michael acceptor ability of these methylenecyclopropane esters has been used towards the synthesis of optically active β amino acids. The nucleophile used in this reaction was an optically active oxazolidinone.[22b] In order to synthesize donor-

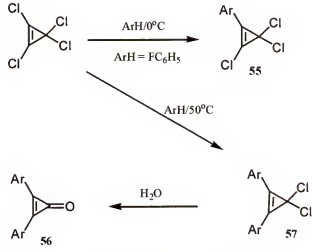
substituted vinyl cyclopropanes de Meijere found that vinyl acetate reacted with tetrachlorocyclopropene to afford the corresponding cyclopropane however the reaction fails with ethyl vinyl ether and other vinyl ethers. In the case of vinyl ethers polymerization was observed.[22c]

**Reactions Involving Cyclopropenium ions from Halogenated Cyclopropenes**

Cyclopropenium cation is the smallest member of the Hückel aromatic systems. Thus, the cyclopropenium cation shows significant stability and reactivity as compared to other carbocations. The cation has $2\pi$ electrons that are delocalized over three p orbitals and suffers from significant strain. Breslow et al. reported the first synthesis of the triphenylcyclopropenium cation.[23a] The development of the chemistry in this field started largely due to curiosity and theoretical interest in these molecules. Nonetheless, the cyclopropenium cations and related systems have found applicability in synthetic organic chemistry.[23b] The trichlorocyclopropenium cation was first prepared and its properties were described by West et al.[23c, d] The resulting cation was shown by West et al.[24a] to be reactive towards various nucleophiles to afford various substituted cyclopropenes. This work by the West group is considered seminal as it opened a way towards the synthesis of several cyclopropyl systems including those that contain heteroatoms and metals. This section will deal with the chemistry that has been reported with perhalogenated cyclopropenium cations specifically those that are obtained from tetrachloro and tetrabromocyclo-propenes.

Treatment of tetrachlorocyclopropene with fluorobenzene in the presence of aluminum chloride at 0°C afforded the monoarylated product (**55**). The reaction when carried out at higher temperatures afforded the bis arylated product (**57**).[24a] This Friedel

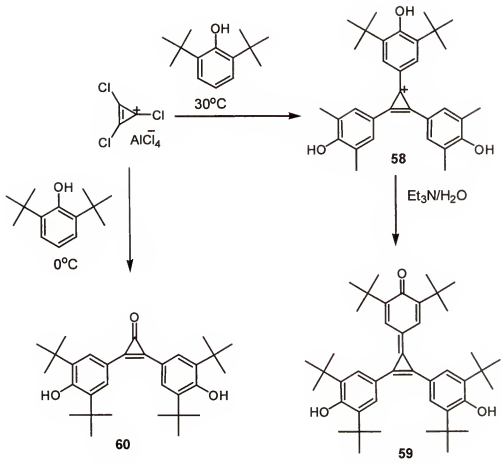
Crafts alkylation was found to proceed in a stepwise fashion, highly activated aryl compounds affording the triarylated cyclopropenium salts.[24b-d]




Scheme 1.19. Arylation reactions of tetrachlorocyclopropene

This was an important discovery as several other alkyl and aryl groups have been appended onto the cyclopropene system by using this methodology (Scheme 1.19). Hydrolysis of the bis arylated product afford the correspond cyclopropeneone (**56**). The hydrolysis of tetrachlorocyclopropene to dichlorocyclopropenone has also been reported. The compound was found to be explosive when prepared in large quantities.

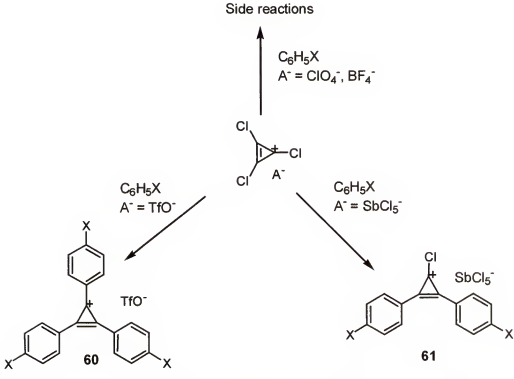
West's group demonstrated the versatility of this reaction when they showed that this Friedel crafts reaction could be performed using various phenols and 2,6-substituted anisole. The triarylcyclopropenium compounds obtained from the reaction between tetrachloro-cyclopropene and 2,6 dialkyl phenols were found to undergo facile oxidation under mild conditions to the corresponding diarylquinocyclopropenes, triquinocyclopropanes.[25a-d]




Scheme 1.20. Triarylated products from tetrachlorocylopropene

The level of arylation of the cyclopropene was controlled by the temperature of the reaction (Scheme 1.20). Diaryliminocyclopropenes were also synthesized in an analogous fashion using 2,6 dialkyl anilines.[25e] Arylation reactions of tetrabromocyclopropene gave analogous tribromomonoaryl cyclopropenes but these compounds have not been studied extensively. Diarylquinocyclopropenes and Diaryliminocyclopropenes are compounds are brightly colored (due to high degree of conjugation) have unusual redox properties. These compounds therefore have possible use in semiconductors, polymers, and dyes. There are a few examples in the recent literature that deal with the synthesis of similar compounds starting with tetrachlorocyclopropene and other aromatic and heteroaromatic phenols.[26a, b]

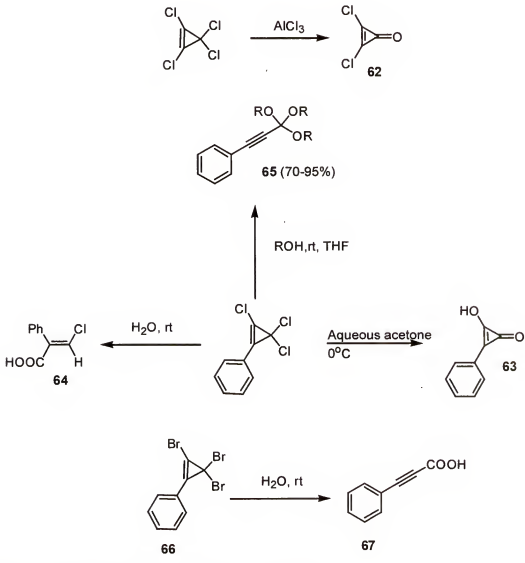
Weiss et al.[27] have studied the nature of the counter ion and its effect on arylation. As mentioned previously unactivated aryl systems gave only the bis arylated cyclopropenes in the presence of aluminum chloride.




Scheme 1.21. Effect of counter ion on arylation of trichlorocyclopropenium ion

Weiss lab was able to demonstrate that if the counter ion were to be changed to triflate then unactivated aromatics such as benzene and fluorobenzene afforded the corresponding triarylated compounds on the other hand hexachloroantimonate resulted in the exclusive formation of bis arylated products (Scheme1.21). The hydrolysis of tetrachlorocyclopropene in the presence of aluminum chloride affords the dichlorocyclopropenone, a compound that was found to be a dangerously unstable[28]. Hydrolysis of aryltrichlorocyclopropenes and aryltribromo-cyclopropenes has been reported. The products obtained depend on reaction conditions. Thus, hydrolysis of

phenyltrichlorocyclopropene in aqueous acetone[29] at 0°C affords the corresponding phenylhydroxycyclopropenones.




Scheme 1.22. Hydrolysis of halogenated cyclopropenes

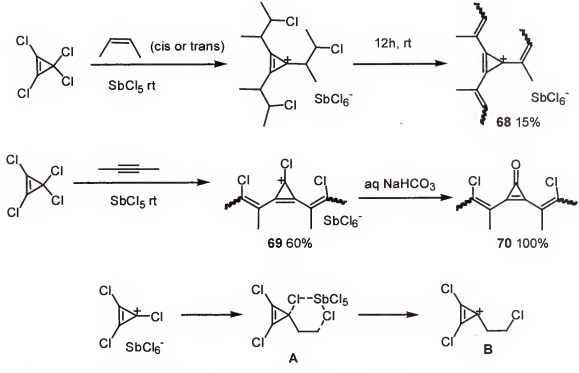
The aryltrichlorocyclopropenes upon exposure to air at room temperature underwent hydrolysis to afford 2-aryl-3-chloracrylic acids whereas the corresponding bromo compounds afford aryl propiolic acids as the sole product.[30] Detty et al.[31] have

reported that alcoholysis of the aryltrichlorocyclopropene followed by mild hydrolysis affords the propiolic acids in excellent yields (Scheme 1.22).

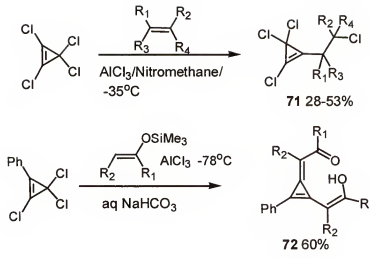
The addition of olefins to trichlorocyclopropenium cation has been investigated. These reactions have been found to be very sensitive to the nature of the counter ion and therefore on nature of the Lewis acid used in the reaction. Weiss[27] was able to demonstrate that for simple olefins, such as 2-butene, and 2-methyl-propene, use of aluminum chloride or silver triflate to generate the cyclopropenium ion did not afford substitution products and polymerization was observed. The reaction when performed using hexachloroantimonate as the anion the olefins reacted smoothly to afford the trisubstituted products (**68**).

The yield of these products was low at room temperature and showed modest improvement when the reactions were carried out at 0°C. The mechanism suggested by Weiss involves the stepwise addition of the olefin to the cyclopropenium cation that is stabilized by antimony anion via a six-center transition state **A** that leads to the formation of reactions intermediates such as **B**. Whereas, such stabilization is not possible when triflate is used as the anion and therefore one does not observe any alkylation. The addition of cis or trans butene gave the same product the formation of the intermediate (**B**) was observed by NMR thus lending further strength to their arguments with regards to the nature of the reaction. The authors mention that aluminum chloride should also be able to promote such a substitution. Addition of alkynes to trichlorocyclopropenium hexachloroantimonate was also investigated by Weiss[27] these reactions afforded the disubstituted products (**69**).[27] The resulting compounds were then easily hydrolyzed to the corresponding cyclopropenones (**70**) (Scheme 1.23).

The viability of Aluminum trichloride catalyzed reaction to afford alkylation products was demonstrated by Musigmann and Mayr.[32] These reactions were carried out with various olefins in the presence of aluminum chloride in nitromethane as solvent at -35°C and exclusively obtained the monosubstituted cyclopropenes (**71**). The use of enol ethers as nucleophiles was explored by Eicher et al.[33] who were able to synthesize a new class of stabilized methylene cyclopropenes also known as triafulvenes (**72**) (Scheme 1.24).

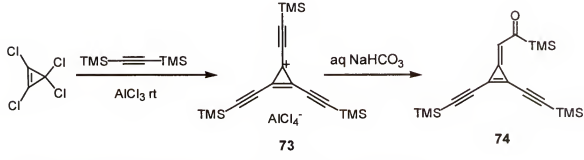



Scheme 1.23. Reactions of tetrachlorocyclopropene with olefins




Scheme 1.24. Reactions of tetrachlorocyclopropene with olefins

The reaction of tetrachloroaluminate salt of **2** with bis(trimethylsilyl) acetylene followed by hydrolysis of the resulting trialkylated cyclopropenium salt **73** leads to the formation of triafulvenes **74** in good yields(Scheme 1.25).



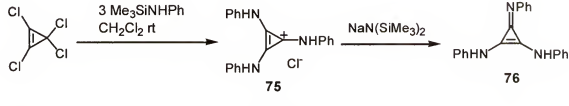

Scheme 1.25. Reactions of alkynes with tetrachlorocyclopropene

The tribromo[1]- and trifluoro-[34a, b] cyclopropenium cations have been reported but the chemistry of these cations has not been studied in as much detail as the trichloro cation. Tetrafluorocyclopropene is highly explosive and this limits its utility in synthetic organic chemistry. The literature mostly pertains to the study of the vibrational spectra of the perfluorocyclopropenium ion. Tetraiodocyclopropene[2c, d] as mentioned previously was synthesized by Weiss and was found to exist in its ionic form. It undergoes

sequential substitution with dimethyl sulfide and trimethylsilyldimethyl amine to afford the correspond sulfur and aza substituted cyclopropenes. The highly explosive nature of this molecule precludes it from being useful in preparative organic synthesis.

**Nucleophilic Substitutions with Tetrahalocyclopropenes**

The reactions of tetrachlorocyclopropene have not been limited to addition of aryl and olefins as nucleophiles. Several nucleophilic reagents containing nitrogen, sulfur, silicon and oxygen have been used effectively. The mechanism of these reactions in many cases need not involve the cyclopropenium ion especially in the case of reactions as lewis acids are not used in these reactions. The mechanism proposed by Yoshida for these substitutions is $S_N2'$ and in the case of tetrabromocyclopropene $S_N1$.[35a] The aza analog of deltic acid was first synthesized by Weiss [35b, 36]. The synthesized involved the treatment of tetrachlorocyclopropene with trimethylsilylaniline to afford the tris(mono-phenylamino)-cyclopropenium chloride (**75**). The resulting salt was deprotonated using sodium hexamethyldisilyazide to afford the aza analog of deltic acid (**76**) (Scheme 1.26).

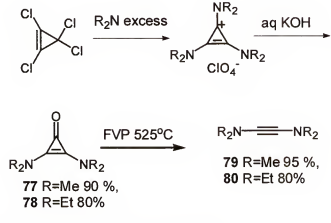



Scheme 1.26. Synthesis of Azadeltic acid analogs

This method gives better yields as compared to Yoshida's protocol that involves use of secondary amines in excess as nucleophiles. The product was found to be thermally unstable but could be stored for weeks with out decomposition at -30°C. An elegant synthesis of Bis-dialkyaminoacetylenes was reported by Breslow et al.[37] Tetrachlorocyclopropene was treated with excess diethylamine to afford the tris

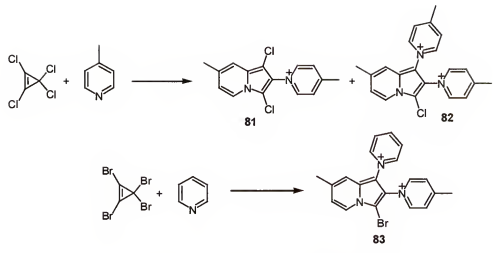
diethylaminocyclopropenyl cation (isolated as the perchlorate). Hydrolysis of this salt in 15% aq KOH at 60-65°C afforded the cyclopropeneone that was subjected to pyrolysis to afford the bis diethylamino acetylene in good yields (Scheme 1.27). Yoshida[38] has also been reported addition of amines to **2**.

The reaction of pyridines with tetrachlorocyclopropene leads to the formation of mono substituted and bis substituted indolizines (**81,82**) (Scheme 1.28). This reactions has been studied in detail by Streitwieser et al. [39a-c]

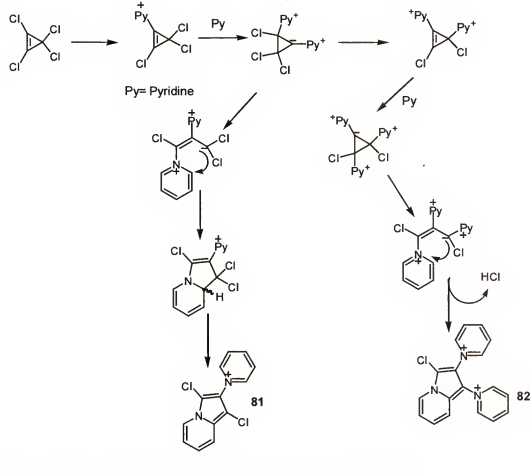



Scheme 1.27. Breslow's Synthesis of diaminoalkynes

Pyridines that have electron-donating groups also give Indolizines whereas pyridines having electron withdrawing groups do not give these products. Similar reaction with tetrabromocyclopropene afforded the bis substituted indolizine (**83**) as the sole product. The mechanism proposed by Streitwieser's group for the formation of these compounds is given in Scheme 1.29.

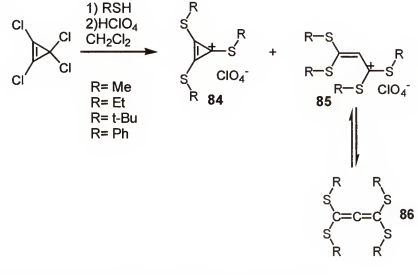



Scheme 1.28. Reactions of pyridines with tetrachlorocyclopropene




Scheme 1.29. Proposed mechanism for the formation of Indolizines

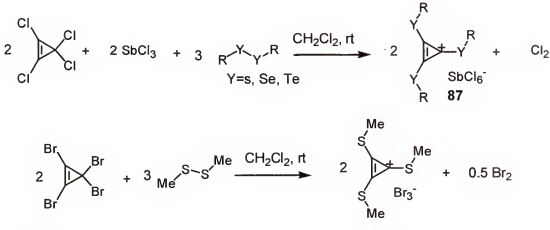
The addition of sulfur nucleophiles to tetrachlorocyclopropene have been reported by Gompper,[40a, b] Yoshida[41] and R. Weiss.[42a-c] Gompper[40a, b] was able to show that addition of various thiols to tetrachlorocyclopropene proceeds to afford the tri substituted cyclopropenium cations. The yields of these compounds were modest at best and poor in certain cases. 1,1,3,3-tetra substituted allylic cations were observed as the side products. These allylic compounds upon treatment with sodium hydride afforded the corresponding allenes (Scheme 1.30).




Scheme 1.30. Reaction of thiols with tetrachlorocyclopropene

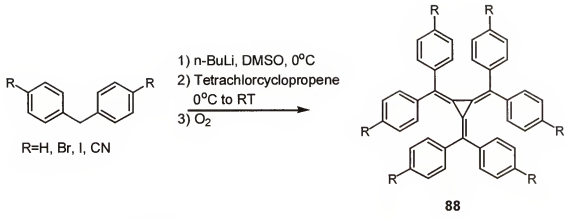
Yoshida's[41] protocol involves the use of Silver tetrafluoroborate to generate the cyclopropenium ion in the presence of thiols to afford the corresponding tristhiocyclopropenium (**84**) cations as the tetrafluoroborate salts. The yields for these compounds by this method were 26-38%. A preparative method for making such compounds has been reported by Weiss et al.[2a-c] Thus, tetrachlorocyclopropene was treated with organic disulfides, diselenides and ditellurides to afford the corresponding trisubstituted cyclopropenium salts in very high yields. The tellurium compounds were found to be

unstable. The product obtained from methyl ditelluride was found to undergo slow decomposition with formation of elemental tellurium. Diphenyl ditelluride did not give any reaction. In addition, the sulfur analog was hydrolyzed under mild conditions to afford the thiodeltic acid as its dimethyl ester. The reaction of tetrabromocyclopropene with methyl disulfide was found to proceed at room temperature in dichloromethane and did not require any acid or silver salts. The resulting product was found to be the tristhiocyclopropenium tribromide. In addition, formation of elemental bromine was also observed. The reaction showed remarkable rate acceleration when the solvent was changed to acetonitrile (Scheme 1.31).




Scheme 1.31. Reactions of Disulfides and Diselenides with tetrachlorocyclopropene

The addition of diphenylmethane anions to tetrachlorocyclopropene has been studied by Fukunaga et al.[43] and Oda et al.[44a] The products obtained from this reactions have been characterized as hexaaryl[3]radialenes (Scheme 1.32). The yields of these products are modest to good. The physico-chemical properties of these compounds have been reported by Oda's group.[44b]




Scheme 1.32. Addition of carbanions to tetrachlorocyclopropene

**Conclusion**

The tetrahalocyclopropenes, especially tetrachloro and tetrabromo, are valuable synthetic intermediates. They are readily accessible from commercially available starting materials. The different types of cycloaddition, cationic and anionic reactions that perhalocyclopropenes can participate in have been reviewed, thus indicating the utility of these compounds in organic synthesis.

CHAPTER 2
DIELS ALDER REACTION OF TETRABROMOCYCLOPROPENE AND 2,5-DIMETHYLFURAN: STRUCTURE AND REARRANGEMENT STUDIES

**Introduction**

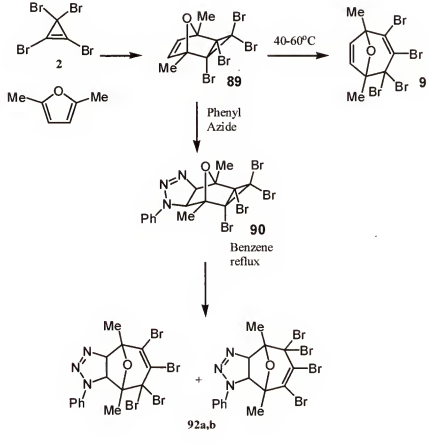
The ability of tetrahalocyclopropenes to take part in Diels-Alder reaction was first reported by Tobey and Law[3a-c] in a series of seminal papers. This remarkable reaction involves an initial [4+2] cycloaddition that leads to the formation of a primary adduct that eventually undergoes a disrotatory ring expansion with a concomitant rearrangement of the halides to afford the corresponding 3.2.1 bicyclic systems. The driving force for the rearrangement is the relief of ring strain associated with the 8-oxa-tricyclo[3.2.1.$0^{2,4}$]oct-6-ene. This reaction is of synthetic importance because it introduces a three-carbon fragment into the ends of a dienophile. The oxabicyclic compounds are of interest as potential synthons as these compounds[44] are easily subjected to further functionalization due to the available halogens on these molecules.

Prior to Tobey's report, it was well known that the parent hydrocarbon cyclopropene does undergo Diels-Alder reaction with cyclopentadiene and that the 3,3-disubstituted cyclopropenes fail to undergo the same reaction.[4] This lead to the supposition that the cycloaddition reactions of cyclopropenes in general prefer *endo* adduction and that alkyl groups at the 3 position lead to unfavorable steric interactions in the transition state and therefore 3,3-dialkylcyclopropenes do not participate in the reaction. In light of the above observations, the facile reactivity of tetrahalocyclopropenes in [4+2] reactions reported was considered interesting and

intriguing. It was also determined by competition experiments that the tetrahalocyclopropenes are less reactive compared to cyclopropene, and that tetrabromocyclopropene is more reactive than tetrachlorocyclopropene and that 3,3-difluoro cyclopropene is slower reactants than tetrabromo and tetrachlorocyclopropene. Thus, the relative rate enhancement observed with larger halogen atoms on the cyclopropene seemed to contradict the possibility of *endo* adduction. In addition, Tobey had performed an elegant experiment wherein 1,2,3-trichloro-3-fluorocyclopropene was treated with furan.[3] This lead to the formation of two products one of the products being the rearranged compound and the other being the unrearranged compound. The formation of the two products were explained on the basis of ability of chloride as good leaving group as opposed to the leaving group ability of fluorine. However, the authors did not establish the stereochemical nature of the primary adduct. Since then several investigators have shown that the initial adduct formed in many of these reactions is *exo*[4a-i].

During the course of our work, that involved the Diels Alder reaction of tetrabromocyclopropene with furans, we observed that if the reaction between 2,5-dimethyl furan and tetrabromocyclopropene were to be carried out at 0°C a crystalline material is obtained. The structure of this compound was established as being the primary adduct (**89**). The assessment of compound **89** as being the primary adduct was based on the $^{1}$H-NMR and the $^{13}$C-NMR. The spectra of this compound were very simple in that the olefinic and the methyl region in the $^{1}$H NMR had only one signal each and the carbon spectrum showed five signals. These observations are easily explained by the structure **89** as it has a plane of symmetry. When **89** was refluxed in benzene it was

quantitatively converted to **91**. This established the identity of **89** as the primary intermediate. The isolation of **89** was interesting as this was the first time that the primary adduct had been observed and isolated especially in the case of tetrabromocyclopropene(Scheme2.1).[5] The stability of this compound is perhaps enhanced by the presence of the methyl groups on the bridgehead carbons as they offer steric hindrance during the disrotatory ring opening of the cyclopropane.




Scheme 2.1. Reaction of tetrabromocyclopropene with 2,5-dimethylfuran

In order to determine the relative stereochemistry by X-ray crystallography several attempts were made to grow crystals of this compound. However all attempts failed to give us quality crystals, in addition it was observed that the compound in solutions had a

tendency to slowly rearrange to the [3.2.1] oxabicyclic compound (**91**). This problem was solved by subjecting **89** to a 1,3-dipolar reaction with phenyl azide.[45] The resulting triazole (**90**) was obtained as a crystalline compound that was relatively stable at room temperature and proffered crystals with good diffraction (Figure 2.1).

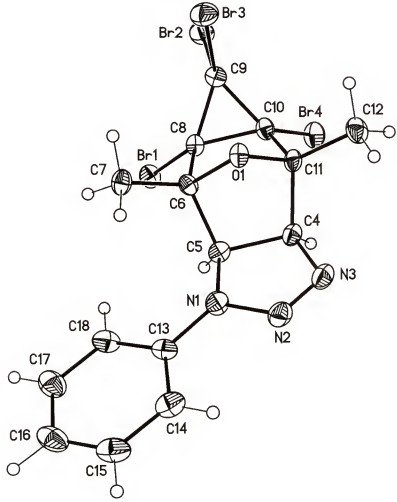



Figure 2.1. X-ray of **90**

The X-ray crystallographic analysis of the compound showed that the geminal dibromo group is *exo* as is the triazole ring. This demonstrates that the primary adduct is formed by *exo* adduction and that the 1,3-dipolar reaction furnishes the *exo* triazole.

The rearrangement of **90** affords products **92a** and **92b** in a ratio 1:1. The assignment, of the H1 and C13 chemical shifts for these compounds, in toluene at 25 °C, was based on H1-C13 direct and long range couplings and on nOe's, is given in Figure 2.2.

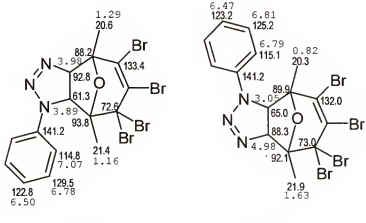
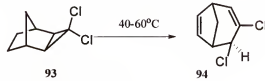



Figure. 2.2: H1 and C13 chemical shifts for compounds **92 a** and **b**.

**Kinetic Data, Results and Discussion**

The solvolysis of cyclopropyl tosylates as well as the rearrangement of dihalocyclopropanes has been studied quite extensively.[46] Creary et al.[47] have compared the solvolysis rates of *endo* tricyclo[3.2.1$^{2,4}$]octane-*exo*-yl triflate and *endo* tricyclo[3.2.1$^{2,4}$]oct-6-ene-*exo*-yl triflate. The conclusion was that the distal double bond participates in stabilizing the resulting positive charge during solvolysis, thus leading to rate acceleration. This was further verified by identification of various products in which the carbon skeleton had undergone rearrangement.[48] In most cases involving gem

dihalocyclopropanes (especially dichloro and dibromo compounds) the reactions involved silver assisted generation of the cation and quantifying and establishing the structures of the products thus obtained.[49] The thermal conversions of 6,6-difluorobicyclo[3.1.0]hex-2-ene and related benzo systems have been studied by Dolbier et al.[50] The 6,6-difluorobicyclo[3.1.0]hex-2-enes was found to under go dehydrofluorinative aromatization through a diradial process where as the corresponding benzo analogs were found to undergo dehydrofluorinative aromatization via the formation of a discrete cation. In the above cases, one of the halogens from the starting material is irreversibly removed and is not recaptured by the resulting cation. Thus, the rearrangement of **89** to **91** and **90** to **92** constitute a special case in the rearrangement of fused cyclopropyl systems. The only reported kinetic data, that is similar to the system that we have investigated, was reported by De Selms' (Scheme 2.2).[51]




**93** **94**

Scheme 2.2. De Selms' rearrangement study

Wherein the authors had reported the addition of dichlorocarbene to norbornylene thus affording 3,3-dichloro-*exo*-tricyclo[3.2.1.$0^{2,4}$]-oct-6-ene (**93**) which was found to under go thermal rearrangement in a facile manner to the *exo*-3,4-dichloro-bicyclo[3.2.1]oct-2-ene (**94**). It is also important to note that the authors do mention that the corresponding reaction of dibromocarbene with norbornylene invariably leads to the corresponding rearranged products; similar observations have been reported by Jeffords et al.[49b] with dibromocarbene additions to bicyclic olefins. Therefore, this is the first example of a [3.2.1.$0^{2,4}$] tricyclic system that contains a gem dibromo group in it that has

lent itself towards kinetic studies. The rearrangement reactions of **89** and **90** were determined by monitoring the reactions by NMR. The activation parameters are given in Table 2.1 and the measured first order rate constants are given in Table 2.2

Table: 2.1. Activation parameters for the rearrangement reactions of **89** and **90**.

| Compd. | Solvent | *ΔH (kcal/mole)* | *ΔS (cal/mole/K)* | *ΔG (kcal/mole)* |
|---|---|---|---|---|
| **89** | toluene-*d8* | 24.59 | -7.88 | 27.06 |
| **89** | DMF-*d7* | 21.23 | -9.59 | 24.04 |
| **90** | toluene-*d8* | 24.79 | -8.04 | 27.32 |
| **90** | DMF-*d7* | 21.81 | -7.31 | 23.95 |

Table: 2.2. First order rate constants for the rearrangement of **89** and **90**

| solvent | toluene-d8 | | DMF-d7 | |
|---|---|---|---|---|
| compd. | T°C | *k* | T°C | *k* |
| **89** | | | 19.2 | 6.6975E-06 |
| | 40.7 | 9.3065E-07 | 40.3 | 7.9800E-05 |
| | 62.6 | 1.2555E-05 | 62.2 | 8.0100E-04 |
| | 84.4 | 1.3175E-04 | 83.4 | 5.8520E-03 |
| **90** | | | 19.6 | 8.0514E-06 |
| | 41.2 | 6.4245E-07 | 41.7 | 1.1001E-04 |
| | 62.7 | 9.1356E-06 | 62.8 | 1.1568E-03 |
| | 84.7 | 9.1097E-05 | | |

Several important conclusions can be drawn with regards to this reaction. Compounds **89** and **90** display basically the same activation parameters and first order rates for the rearrangement, indicating that the distal double bond in these tricyclo[3.2.1.$0^{2,4}$] compounds bear little consequence towards the rearrangement as opposed to the effects observed by Creary. In fact the *k* for **90** is about 1.5 times that of **89**. The 1:1 ratio of **92a** and **92b** formed during the course of rearrangement suggests that the triazole does not have a significant effect on the reaction. The first order rate

constants that were observed for **89** in toluene at 40ºC and 60ºC are $9.3X10^{-7}$ and $1.25X10^{-5}$ respectively. These values are very close to the rate constants observed by De Selms for the rearrangement of **93** to **94** (Scheme **2.2**). The reported *k* value in carbon tetrachloride, for the rearrangement of **93** at 60ºC, is $1.98X10^{-5}$. The rates for **89** in DMF at 20ºC and 40ºC are $6.7X10^{-6}$ and $7.98X10^{-5}$ respectively. The reported *k* value for the rearrangement of **93** in acetonitrile at 20ºC is $1.62X10^{-4}$. It is interesting to note that De Selms' compound (**93**) is slightly faster in reactivity compared to **89**, in non polar solvents.[52] However, in polar solvents, De Selms' compound is 24 times faster in rearrangement as compared to **89**. One would expect bromine to ionize in a more facile manner compared to chlorine and should therefore show significantly higher rates of reaction. The slower rates observed for **89** as compared to **93** can be explained if one were to assume that the bridgehead methyl groups provide steric hindrance during the disrotatory process of ring expansion of **89**. This would also imply that the cleavage of the carbon bromine bond is perhaps attended by the breaking of the σ bond. In addition, the $k_{DMF}/k_{toluene} = 85$ for **89**, and the $k_{DMF}/k_{toluene} = 173$ for **90**, this suggests a significant development of charge at the transition state. Thus, a diradical mechanism for this rearrangement can be ruled out.[14] The $\Delta\Delta S$ for this reaction going from toluene to DMF is about 1.7 eu. The small value implies that the reaction does not involve the rearrangement of the solvent sphere around the reacting molecule in its transition state.

All of the above observation leads one to believe that the rearrangement of **89** to **91** and **90** to **92a,b** involves the ionization of the *endo* bromine. The exact nature of the developing cation cannot be explained however one can assume that either an intimate ion pair or partially developed positive charge that is assisted by the breaking σ bond can

be considered as reasonable mechanisms. It is highly unlikely that a cyclopropyl cation is formed that subsequently undergoes rearrangement.

## Experimental

**General Methods**. All solvents used in the reactions were distilled prior to use. 2,5-Dimethyl furan was obtained from Aldrich and distilled prior to use. Tetrabromocyclopropene was synthesized as per the literature procedure and was distilled twice before using it in the Diels-Alder. Subsequent reactions resulted in compounds that were pure for kinetic studies. Melting points were obtained, on a Thomas-Hoover Capillary Melting point apparatus, and are reported uncorrected. IR spectra were recorded on a FT-IR spectrometer. NMR spectra were recorded on a Varian spectrometer operating at 300 MHz for $^{1}H$ and at 75 MHz for $^{13}C$. Chemical shifts are reported in ppm relative to TMS.NMR spectra were obtained on Varian 300 MHz spectrometer; chemical shifts are reported in δ units relative to tetramethylsilane (TMS) signal at 0.00 ppm. Coupling constants are reported in Hertz.

**2,3,3,4-Tetrabromo-1, 5-dimethyl-8-oxa-tricyclo[3.2.1.0$^{2,4}$]oct-6-ene (89).**

Tetrabromocyclopropene (1.4g, 0.0039 mols) was taken in a sealed tube and cooled in an ice bath. 2,5-dimethylfuran (0.46g, 0.0048 mols) was added to the tetrabromocyclopropene. The resulting mixture was kept in the ice bath and stirred with the help of a magnetic stir bar. The solution gradually turns into pale brown semi solid. The reaction mixture was subjected to column chromatography on silica gel and the product was eluted using 10% methylene chloride in hexane. The solvent, in the fractions containing the product, was removed under reduced pressure at room temperature (higher temperatures lead to significant rearrangement of the product). The product was obtained as a colorless solid (1.5g, 84%). mp 110-112°C.

$^1$H NMR (300 MHz, $CDCl_3$) δ 6.55 (s, 2H), 1.82(s, 6H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 144.6, 91.4, 60.8, 45.6, 14.6. IR (NaCl) $cm^{-1}$ 2984, 1563, 1381, 1125, 960, 906, 718.

Anal. Calcd for $C_9H_8Br_4O$: C, 23.93; H, 1.78. Found C, 24.18; H, 1.75.

**Rearrangement of 3 to 5:**

100 mg of **89** was taken and dissolved in 5 mL of dry benzene And refluxed for 3 hours. The benzene was removed under reduced pressure to afford 100 mg of **91**.

$^1$H NMR (300 MHz, $CDCl_3$) δ 6.50 (d, J= 5.5 Hz, 1H), 6.25 (d, J= 5.5 Hz, 1H), 1.93 (s, 3H), 1.68 (s, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 141.10, 135.5, 133.1, 128.5, 93.2, 89.5, 71.1, 23.9, 22.1. IR (NaCl) $cm^{-1}$2985, 2935, 1564, 1444, 1377, 1306, 1159, 1090, 942, 869, 758, 726, 714.

An analytically pure sample was obtained by sublimation. mp 30-32°C. Anal. Calcd for $C_9H_8Br_4O$: C, 23.93; H, 1.78. Found C, 24.35; H, 1.75.

**Synthesis of triazole (90)**

In a 5 mL, rb flask 0.407g (0.9 mmols) of 3 was taken and dissolved in 1mL of methylene chloride. Phenyl azide (0.119g, 1 mmol) was added to the above mixture and stirred at room temperature for 2 days. The methylene chloride was allowed to evaporate slowly at room temperature when colorless crystals of the product were obtained. The crystals were washed with 20% ether in pentane to remove excess pheny azide and recrystallized from 20% ether in pentane. The first crop of crystals weighed 240 mg. The mother liquors were subjected to recrystallization to afford an additional 220 mg of **90**. mp 129-130ºC (with violent decomposition).

$^1$H NMR (300 MHz, $CDCl_3$) δ 7.20-6.80(m, 5H), 4.92 (d, J= 8.79 Hz), 4.02 (d, J= 8.79 Hz), 1.70 (s, 3H), 1.30 (s, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 141.1, 129.7, 123.4, 114.8, 91.8, 90.53, 90.51, 63.5, 55.4, 54.9, 34.6, 13.5. IR (NaCl) $cm^{-1}$ 1599, 1494, 1380, 1355, 965, 750, 690.

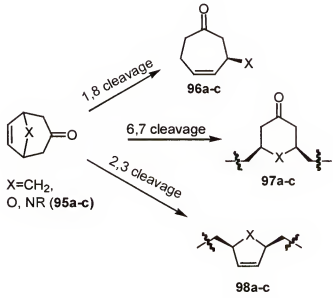
An analytically pure sample was obtained by recrystalizing the compound from 20% ether in pentanes. Anal. Calcd for $C_{15}H_{13}Br_4N_3O$: C, 31.56; H, 2.30. Found C, 31.62; H, 2.29.

The kinetic data is reported in Appendix A.

CHAPTER 3
FUNCTIONALIZATION OF TETRAHALOCYCLOPROPENE CYCLOADDUCTS BY SILVER PROMOTED REACTIONS

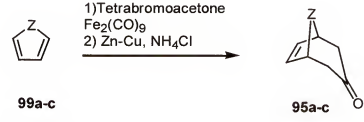
**Introduction**

The bicyclo[3.2.1]octane systems **95a-c** have found wide spread use as key intermediates in the synthesis of natural products and other compounds.[54] Embedded within these building blocks are various cycloheptenone **96a-c**, 4-pyrone **97a,** 4-piperidone **97b**, cyclohexanone **97c**, dihydrofuran **98a**, dihydropyrrole **98b**, and cyclopentene **98c** ring systems which are common to a wide array of natural products. Each of these ring systems can be unveiled by the cleavage of one of the three unique bridges in the bicyclic molecule (Scheme 3.1).




Scheme 3.1.Possible transformations of [3.2.1]bicyclic systems

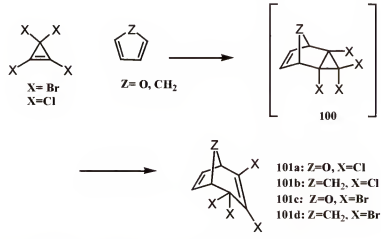
The parent derivatives are typically prepared via the cycloaddition of an oxyallyl cation equivalent to cyclic dienes **5a-c** (furan, pyrrole, cyclopentadiene). This reaction was popularized by Noyori and co-workers,[55] their procedure involved generating the oxyallyl cation from tribromoacetone and diiron nonacarbonyl (Scheme 3.2). Other methods of oxyallyl cation generation have also been reported[56] although all typically rely on the use of halogen atoms to stabilize the oxyallyl cation intermediate. These halogens are subsequently removed under reducing conditions to produce the bicyclo[3.2.1]oct-6-ene-3-ones, meso compounds that have found wide use in organic synthesis.[57]




Scheme 3.2. Oxyallyl cation approach to [3.2.1]bicyclic systems

Although the oxyallyl cation addition is the method of choice for gaining entry into this family of bridged compounds, there were in fact earlier reports of these types of derivatives accessed though alternative cycloaddition reactions. In 1967, Tobey and Law[3] reported the reaction of furan, substituted furans, and cyclopentadiene with tetrachloro- and tetrabromocyclopropene (Scheme 3.3). They proposed that the tetrahalocyclopropenes underwent an initial Diels-Alder cycloaddition with the cyclic dienes to produce the cyclopropyl norbornene derivatives **100**. These workers were unable to isolate the primary cycloadducts. Instead, they observed that the primary

adducts had undergone a spontaneous rearrangement by way of a halogen atom migration to yield the halogenated derivatives of the bicyclo[3.2.1]octadiene nucleus.




Scheme 3.3. [3.2.1]bicyclic systems from tetrahalocyclopropenes

Although this unusual rearrangement has generated a variety of elegant mechanistic studies,[4,5,6] there has been very little interest in these compounds from a synthetic perspective.

The use of the oxabicyclo[3.2.1]octane for the synthesis of heterocycles[44a] and carbocyles is of considerable interest.[44b,c] It is noteworthy that the resulting adducts **101a/d**, in addition to having the rigid [3.2.1] oxabicyclic or carbocyclic framework, contains three contiguous functionalized carbons that constitute a perhalogenated allylic system. This substitution pattern suggested that it would be possible to further functionalize this system via cationic, anionic, or free radical processes. Thus, these molecules are attractive intermediates for the synthesis of natural products and are complementary to those synthons prepared though the oxyallyl cation route. Initial studies have been focused on the functionalization of the halogenated bridge and in particular, the replacement of the halide groups with oxygen and carbon based

nucleophiles. In this chapter are reported studies on the addition of nucleophiles to the halogenated positions of such bicyclic system.

## Results and Discussion

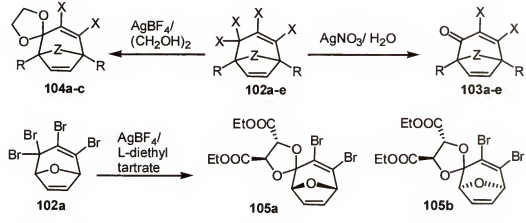
### Silver Promoted Addition of Oxygen Nucleophiles

Initially the formation and trapping of carbocation intermediates by use of a Lewis acid in the presence of latent nucleophiles was examined. It was envisioned that strong Lewis acids could promote the formation of a symmetrical allylic cation and that it should be possible to intercept this cation with a variety of nucleophiles. Useful reactions could only be realized with the use of silver salts.[44a] Other Lewis acids based on copper or aluminum either returned unreacted starting material or promoted extensive decomposition of the tetrahalide.

Silver salts smoothly facilitated the addition of water to the tetrahalides (**102a-e**) to produce the dihaloenones (**103a-e**) in very high yields (Table 3.1). The hydrolysis of the tetrabromo compounds proceeds at room temperature whereas the hydrolysis of the tetrachloro compounds required higher temperatures. This is not surprising and the difference in reactivity can be explained invoking the difference between C-Cl and C-Br bond strengths.

In addition to water, silver ion also promoted the addition of diols to the tetrahalides to produce ketals (Scheme 3.4) **104a-c** that can function as protected derivatives of the enones. Silver tetrafluoroborate was superior to silver nitrate due to the small amounts of water present in the silver nitrate, which lead to a mixture of ketals and ketones. Thus, the formation of ketals by silver tetrafluoroborate was found to be reliable and leading to the exclusive formation of ketals in high yields. The ability to directly form ketals was further explored using L-diethyl tartrate. The resulting ketals would be

diastereomeric and hence ought to be separable by column chromatography. Thus when **102a** was treated with silver tetrafluoroborate and L-diethyl tartrate a 1:1 mixture of the corresponding diastereomeric ketals (**105a,b**) were obtained that were separable by column chromatography. Several attempts were made to hydrolyze these ketals, under a variety of conditions. Unfortunately, none of the conditions explored gave the desired ketones.




Scheme 3.4. Silver mediated synthesis of ketones and ketals

Table 3.1. Silver Promoted Hydrolysis and Alcoholysis of Tetrahalides

| Compd | Z | X | R | conditions[a] | Product | yield[b] |
|---|---|---|---|---|---|---|
| **102a** | O | Br | H | Method A | **103a** | 83% |
| **102b** | O | Br | $CH_3$ | Method A | **103b** | 85% |
| **102c** | $CH_2$ | Br | H | Method A | **103c** | 90% |
| **102d** | O | Cl | H | Method B | **103d** | 84% |
| **102e** | $CH_2$ | Cl | H | Method B | **103e** | 86% |
| **102a** | O | Br | H | Method C | **104a** | 85% |
| **102b** | O | Br | $CH_3$ | Method C | **104b** | 87% |
| **102c** | $CH_2$ | Br | H | Method C | **104c** | 82% |

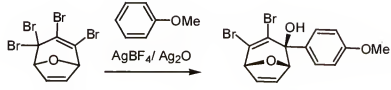
a) Method A: 2 eq. $AgNO_3$, 1:1 acetone: water, 25° C; Method B: 1 eq. $Ag_2O$. 1 eq. $AgNO_3$, 1:1 dioxane: water, reflux; Method C: 2 eq. $AgBF_4$, 2 eq. $(CH_2OH)_2$, $CH_2Cl_2$, -78° C→25° C. b) isolated yield after chromatography.

When the hydrolysis was performed under acidic conditions, the ethyl esters were hydrolyzed to afford the diacids. Extremely strong acids such as perchloric and

concentrated sulfuric acid lead to decomposition of products. Trimethylsilyl bromide and trimethylsilyl iodide did not afford the ketones and only lead to decomposition of the starting material.

**Silver Mediated Addition of Carbon Nucleophiles**

The facile addition of oxygen based nucleophiles, promoted by silver salts, warranted an investigation of the addition of carbon-based nucleophiles to the tetrahalides. It was imagined that moderate nucleophiles such as aromatics, heteroaromatics, and allyl/vinyl silanes would easily add to the allylic cation once generated upon treatment with a Lewis acid. The studies began with the attempted addition of an activated arene, anisole, to the tetrabromo adduct **102a**. Traditional Lewis acids such as aluminum chloride, boron trifluoride etherate or titanium tetrachloride resulted in extensive decomposition of the starting halide. The previous success with silver salts prompted us to examine the reaction of **102a** with anisole and silver tetrafluoroborate. Under these conditions, a complex mixture of products was formed with some evidence of compounds resulting from multiple arylation of the tetrabromide.



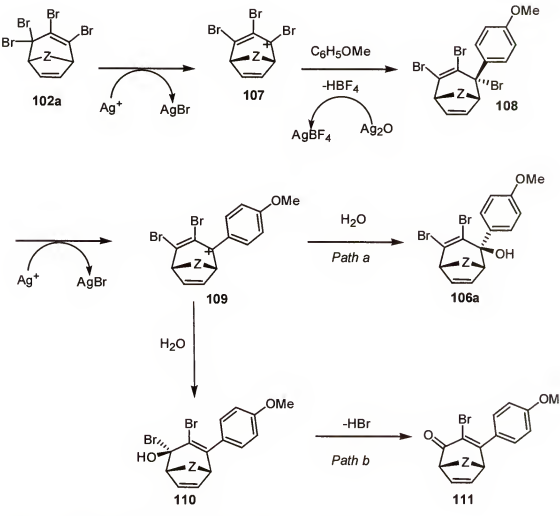

**102a** **106a**

Scheme 3.5. Preliminary arylation studies

There was concern that the extensive decomposition of the materials was related to the production of strong acid ($HBF_4$) during the arylation reaction. In an attempt to scavenge the strong acid produced, silver oxide was added to the reaction mixture. Under

these new conditions a clean conversion to a new adduct **106a** was observed (Scheme 3.5).

The product of this Friedel-Crafts type reaction was determined to be the product of the addition of both a molecule of the arene and a molecule of water.



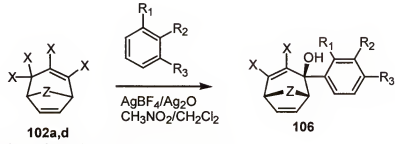

Scheme 3.6. Proposed Mechanism for formation of products

Overall, the reaction consumed two moles of silver ion, suggesting the sequential generation of cations from the tetrabromide. A mechanistic proposal for the formation of these adducts rationalizes the stereochemistry of the arylation (Scheme 3.6).

Initial reaction with silver ion generates the allylic cation **107**, which is attacked by anisole from the less sterically congested *exo*-face to give the transient tribromide **108**. Although not identified, **108** is conceivably one of the products produced in the absence of silver oxide. An equivalent of fluoroboric acid is generated during this process, which reacts with the silver oxide to produce an equivalent of water. Further reaction of **108** with silver ions generates a second allylic cation **109**. It is proposed that bromide **108** is more reactive towards ionization than **102a** because of the extra stabilization in **109** from the pendant aromatic ring. Therefore, if only a single equivalent of silver ion is added to the reaction, a mixture of products would be expected. The allylic cation is preferentially attacked by water (rather than a second molecule of the arene) to produce the tertiary alcohol **106a**. When considering the attack of water on cation **109**, two different outcomes are possible, *path a* leads to the observed product **106a**. Alternatively, attack at the other terminus of the allylic cation (*path b*) would produce bromohydrin **110**, which would be expected to collapse to the enone **111**. Although the enone **108** is the more stable compound (see below), the alcohol forms kinetically, possibly owing to the greater localization of the cationic center at the benzylic position. The ease of conversion of the tetrabromide to an arylated adduct prompted a study of the reaction utilizing a combination of different tetrahalides and aromatic systems (Table 3.2).

Examination of the reaction of the furan adduct **102a** with a variety of arene nucleophiles revealed that only arenes with one or more activating groups were sufficiently nucleophilic to undergo this reaction. Attempts to employ arenes of a more moderate nucleophilicity such as benzene, toluene, or naphthalene resulted simply in the production of the unsubstituted ketone **103a**. It is believed that this product results from

the competitive addition of water to allylic cation **107** with subsequent collapse of the bromohydrin. It appears that only highly activated aromatic rings add to cation **107** faster than water and lead to the arylated products. Placement of a methoxy group was sufficient to promote addition and the arylated products were produced in high yield.




**102a,d** **106**

Table 3.2. Tertiary alcohols obtained by arylation

| Compd[a] | $R_1$ | $R_2$ | $R_3$ | Product | yield[b] |
|---|---|---|---|---|---|
| **102a** | OMe | H | H | **106a** | 87% |
| **102a** | OMe | OMe | H | **106b** | 75% |
| **102a** | OMe | Me | H | **106c** | 70% |
| **102a** | OEt | H | H | **106d** | 82% |
| **102a** | OMe | OMe | OMe | **106e** | 82% |
| **102a** | OMe | Br | H | **106f** | 80% |
| **102a** | OMe | I | H | **106g** | 35% |
| **102d** | OMe | H | H | **106h** | 68% |
| **102d** | OMe | OMe | H | **106i** | 64% |

a) The tetrahalide is treated with 2 eq. $AgBF_4$, 2 eq. $Ag_2O$ and 4 eq. of the aromatic in dichloromethane at –78° C. b) yield refers to the major regioisomer only after purification.

The regiochemistry of the arylation was extremely high with products forming from forming from an almost exclusive addition to the position para to the activating group. Although minor amounts of ortho addition products could be seen in the NMR of the crude material, they were separated by chromatography, giving the pure para compound. The stereochemistry of the tertiary alcohol (**106e**) was confirmed by X-ray analysis of the product, derived form the addition of trimethoxybenzene (Figure 3.1).

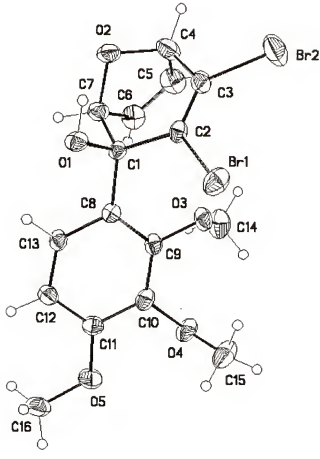
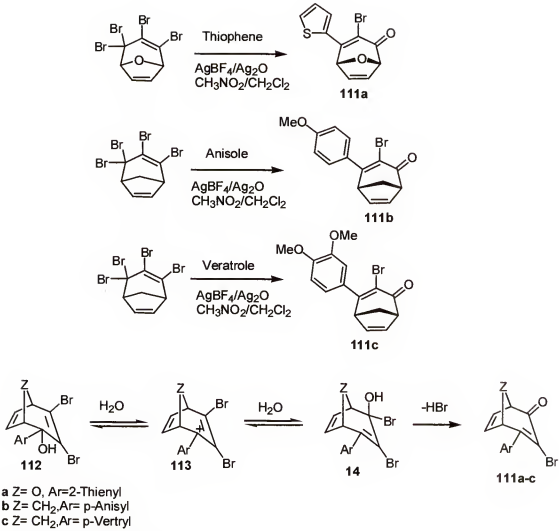



Figure 3.1. X-Ray of **106e**

In some cases, the regioisomeric enones **111a-c** were produced (Scheme 3.7). Silver promoted addition of thiophene to **102a** was observed to initially generate the expected *exo*-alcohol but upon purification by column chromatography, the compound spontaneously rearranged to the ketone **111a**. Tetrabromide **102c**, which contains a carbon rather then oxygen bridge produced the enone derivatives **111b-c** directly upon reaction with anisole or veratrole. Although, on occasions the tertiary alcohol **112a** did survive chromatography and was characterized, compounds **112b-c** have never survived chromatography although evidence of these compounds has been observed in the crude reaction mixture by GC-MS.

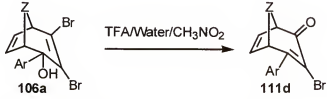



Scheme 3.7. β-Aryl-enones obtained by arylation

This change in product distribution has been attributed to the reversible nature of the addition of water to the allylic cation. It is possible that a catalytic quantity of acid, present either in the reaction mixture or from silica gel, can promote the reversible dehydration of certain tertiary allylic alcohols to the cations **113a-c**.

Although kinetic attack occurs at the more substituted carbocation, addition at the other termini of the allylic cation produces bromohydrins **114a-c**. Rapid and an irreversible loss of hydrobromic acid lead to the thermodynamically favorable aryl

enones **111a-c**. The ease of this conversion likely depends on the stability of the intermediate carbocations. In the case of the thienyl substituent, the stabilization provided by the sulfur atom helps promote ionization of **112a**. The fact that the methylene bridged compounds appeared to directly produce the enone, suggests that the oxobridge in compound **102a** destabilizes the cation, which slows ionization and stabilizes the alcohol. With no such destabilization in **102b-c**, the equilibration takes place easily and directly produces the enones. Since this represents a conversion of a kinetic to a thermodynamic product, it was envisioned that more vigorous conditions could be used to promote the conversion of other adducts to cations related to **113** and other arylated products could be directly converted to the corresponding enones (Scheme 3.8).

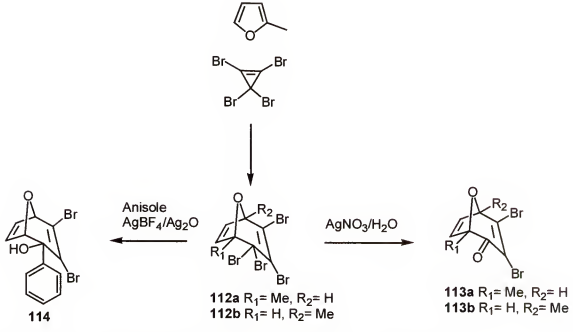



Scheme 3.8. Acid catalyzed rearrangement of tertiary alcohol

This could be demonstrated by reaction of adduct **106a** with trifluoroacetic acid and water in a strongly ionizing solvent to produce enone **111d** in very good yields.

Although the initial halocyclopropene adducts are non-symmetric, the cation produced by ionization is and as such, attack of the arene on either terminus of the allyl system leads to the same product. If a mono-substituted furan were to be used in the initial cycloaddition reaction, arylation of this adduct could lead to two different isomers. To examine if there would be any influence of a bridgehead substituent on the

regioselectivity of the attack of nucleophile, non-symmetric adducts **112a/b** were prepared by cycloaddition with 2-methylfuran and reacted with a nucleophile under silver promoted conditions (Scheme 3.9).




Scheme 3.9. Reaction of 2-methyl furan with tetrabromocyclopropene

Reaction of 2-methyl furan and tetrabromocyclopropene produced a mixture of regioisomeric cycloadducts, **112a/b** in an unassigned 2:1 ratio. Silver promoted hydrolysis of the adducts produced two enones **113a/b** again in a 2:1 ratio with **114** assigned as the major product by NMR. Attempts were made to separate the two compounds by chromatography without any success. This distribution was interpreted as a slight preference for attack of water at the least hindered terminus of the allylic cation and suggested shielding of the allyl system by the bridgehead methyl group. Use of a more demanding nucleophile such as anisole offered much greater levels of selectivity and produced alcohol **114** as the only product, which was assigned by x-ray crystal

(Figure 3.2) analysis thus providing experimental evidence for the degeneracy of the allylic cation that is formed from both **112a** and **112b.**

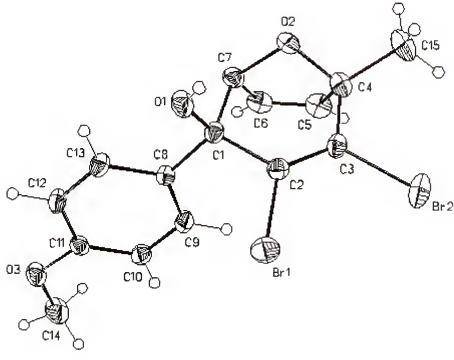


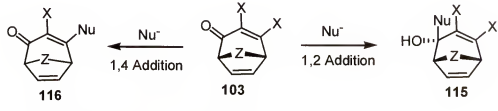

Figure 3.2. Crystal structure of **114**

**Addition of Organometallic Reagents to Dihaloenones 103a and 103c**

Although the addition of highly reactive nucleophiles was possible under the silver promoted additions, it became quite clear that there were severe limitations of this method, i.e. the arenes were limited to only those that were highly activated. In addition, attempts to add other latent nucleophiles such as allyl and vinyl silanes were unproductive. In an attempt to expand the types of nucleophiles that could be added to

these bridged synthons, the addition of more reactive nucleophiles to the readily available ketones **9a-c** was examined (Scheme 3.10).

The dihaloenone derivatives **103a-e**, prepared by direct hydrolysis of the tetrahalides, offer several positions for the addition of highly reactive nucleophiles. 1,2-Addition would lead to tertiary alcohols **115**, diastereomeric to those produced by arylation, while 1,4-addition would produce substituted enones **116** by an addition-elimination mechanism. Little information was available on the addition of powerful nucleophiles such as organometallic reagents to these types of dihaloenones[58] and there would be concern that competing processes such as metal-halogen exchange[59] might be competitive. Gratifyingly, it was found that 1,2-addition of nucleophiles could be accomplished with the correct choice of the organometallic reagent (Table 3.3).

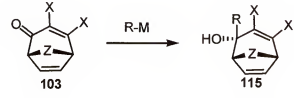



**116** **103** **115**

Scheme 3.10. Addition of nucleophiles to dihaloketones

Addition of hydride under Luche conditions[60] exclusively produced the *endo* alcohols **115a** and **115c**. The reduction of **103b**, however, gave a 1:1 mixture of *exo: endo* alcohols, again demonstrating the shielding effect of the bridgehead methyl group. Attempts to add alkyl groups *via* the corresponding organolithium reagents led only to decomposition of the starting enone. This was presumably due to competitive metal-halogen exchange[61] between butyl or phenyl lithium reagents utilized and the vinyl bromides.

Thus, addition of Grignard reagents, which are less prone to undergo this type of reaction,[62] successfully led to clean 1,2-addition of various carbon nucleophiles. Addition of vinyl, propynyl, phenyl, and naphthyl magnesium bromide produced the corresponding *endo* alcohols **115d-h** in good yields. The addition of the organic fragments appears to have occurred exclusively from the *exo*-face as determined by an x-ray crystallographic study of the acetylide addition product **115e** (Figure 3.3).




**103** **115**

Table3.3. Products obtained by 1,2 addition of nucleophile to dibromoenones

| Compd. | Reagent | Product | R | Yield |
|---|---|---|---|---|
| **103a** | $NaBH_4/CeCl$ | **115a** | H | 95% |
| **103b** | $NaBH_4/CeCl_3$ | **115b** | H | 96% |
| **103c** | $NaBH_4/CeCl_3$ | **115c** | H | 97% |
| **103a** | nBuLi | decomp. | N/A | N/A |
| **103a** | PhLi | decomp. | N/A | N/A |
| **103a** | $H_2C$=CHMgBr | **115d** | $H_2C$=CH | 74% |
| **103a** | $H_3CCCMgBr$ | **115e** | $H_3CCC$ | 92% |
| **103a** | $C_6H_5MgBr$ | **115f** | Ph | 81% |
| **103a** | $C_{10}H_7MgBr$ | **115g** | 1-napthyl | 89% |
| **103a** | $C_4H_3SMgBr$ | **115h** | 2-thiophenyl | 88% |
| **103a** | nBuMgBr | **115a** | H | 90% |
| **103c** | nBuMgBr | **115c** | H | 90% |

Interestingly, the addition of butyl (or hexyl) magnesium bromide failed to produce the desired *endo* alcohol but instead led to the formation of the previously described secondary alcohol **115a**.

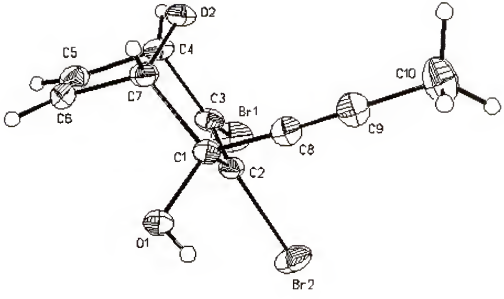


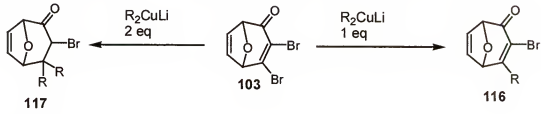

Figure 3.3. X-ray crystal structure of **115e**

This most likely occurs through a β-hydride transfer from the alkyl Grignard reagent[63] (Scheme 3.11). Similar reaction was observed with **103c**, the *endo* alcohol **115c** was obtained exclusively.

Scheme 3.11. Reduction of ketones by alkyl magnesium bromides

In order to circumvent this facile reduction, we turned to the corresponding cerate derivatives[64] which have been shown to be less prone to β-hydride reduction. Unfortunately, addition of the cerate derived from butyl magnesium bromide led only to

the alcohol **115a**. With the successful results of the 1,2-addition process, we next examined the addition of organocuprates to the dibromoenone **8a** (Table 3.4).




Scheme 3.12. Addition of cuprates to dihaloenones

Table 3.4. Addition of Cuprates to dihaloenones

| Entry | Cuprate | Equiv. | Product | R | Yield |
|---|---|---|---|---|---|
| 1 | $Me_2CuLi$ | 1 | **116a** | $CH_3$ | 84% |
| 2 | $Bu_2CuLi$ | 1 | **116b** | Bu | 88% |
| 3 | $Ph_2CuLi$ | 1 | **116c** | Ph | 78% |
| 4 | $Me_2CuLi$ | 2 | **117** | $CH_3$ | 73% |

Addition of one equivalent of the Gilman cuprates derived from methyl, butyl and phenyl lithium effected clean conversion to the β-substituted enones **116a-c** through an addition-elimination sequence (Scheme3.12).

It was also possible to employ two equivalents of the cuprate to effect the sequential addition of two methyl groups to the β-position of the enone to produce **117** as a mixture of *endo* and *exo* bromides[65] resulting from a non-selective protonation of the enolate.

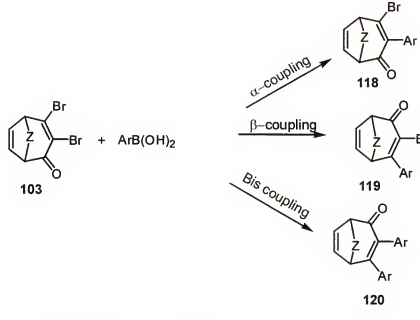
Having successfully explored the reactivity of the oxa[3.2.1]bicyclic dihaloenones with Grignard and Gilman cuprates. We were interested in exploring the reactivity of these dihaloenones in Palladium catalyzed couplings. Palladium catalyzed couplings are perhaps one of the most important method of making carbon-carbon bonds.

These procedures are mild usually require catalytic amounts of the transition metal, give excellent yields and above all these reactions can be tailored to make carbon-carbon bonds with sp, $sp^2$ and $sp^3$ hybridized carbons. The various kinds of palladium catalyzed reactions that are known are the Heck, the Suzuki, the Sonogashira, and Stille reactions, each reaction has its utility towards the synthesis of a desired molecule.[66] The ready availability of the dihaloenones (**103a-e**) prompted us to study the feasibility of palladium catalyzed couplings. The remaining part of this chapter deals with the Suzuki couplings that were carried out on **103a** and **103c** as model compounds.

Suzuki couplings are a class of palladium catalyzed couplings that typically involve the coupling of an aryl boronic acid or vinyl boronic acid to an aryl or vinyl halide. The typical reaction condition involves a mixture of aryl boronic acid, the aryl or vinyl halide, preformed palladium (0) such as tetrakistriphenylphosphine palladium (0) and a base such as potassium carbonate or sodium carbonate. The solvents used for these reactions vary from dimethylformamide to acetonitrile. Palladium couplings using either α-haloenones[67] or β-haloenones,[68] are well documented. However, the use of and α ,β-dihaloenones,[69] such as **9a** and **9c**, are rare. Most of the literature deals with the Stille and Suzuki couplings of 2,3-dibromo[1,4]naphtho-quinones and 2,3-dichloro[1,4]naphthoquinones. Such systems are symmetrical and thus there is no electronic or steric difference in the α and β positions. Thus, the results from such systems cannot be used as a guide to predict the outcome of the products that could be obtained from the palladium reactions involving **103**.

In the case of **103a**, one could envisage the formation of several possible products from the starting materials in question. The coupling could either occur at the α position

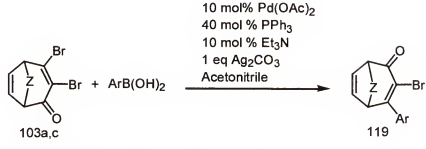
leading to the formation **118** or at the β position affording **119** (Scheme 3.12). The bis coupled compound **120** could also be obtained if two or more equivalents of the aryl boronic acid were to be used.




Scheme 3.12. Possible products from Suzuki coupling

Several conditions were explored using phenyl boronic acid and it was soon found that *in situ* generation of Pd (0) using palladium acetate, triethylamine, triphenyl phosphine and silver carbonate as base gave good to very good yields of the β coupled products. It must be mentioned that when preformed Pd (0) catalyst such as tetrakistriphenylphosphine palladium was used or when the potassium carbonate or sodium carbonate were used as the base, the reaction did not produce any products at room temperature and only starting materials were observed. This points to highly sensitive nature of these reactions to the conditions that are used. The solvent of choice for these reactions was acetonitrile. The reactions were carried out at room temperature. In order to produce the bis coupled product two equivalents of phenyl boronic acid were

used however the bis coupled product was not observed at room temperature. Higher reactions temperatures were utilized but no bis coupled product was observed. An exhaustive survey of various catalysts and ligands needs to be carried out in order to establish the right conditions for selective α coupling as well as for bis coupling reactions. In order to explore the generality of this reaction several aryl boronic acids were subjected to Suzuki coupling with **103a** and **103c** (Scheme 3.13). In all cases, the products were identified as those arising from β coupling (Table 3.5). The isolated yields of the resulting products were good to very good in most cases. All the compounds are colorless crystalline materials that tend to decompose gradually at room temperature but are stable when kept at low temperature away from light.




Scheme 3.13. Suzuki couplings of dibromoenones **103**

Table 3.5. Products obtained from Suzuki coupling of dihaloenones

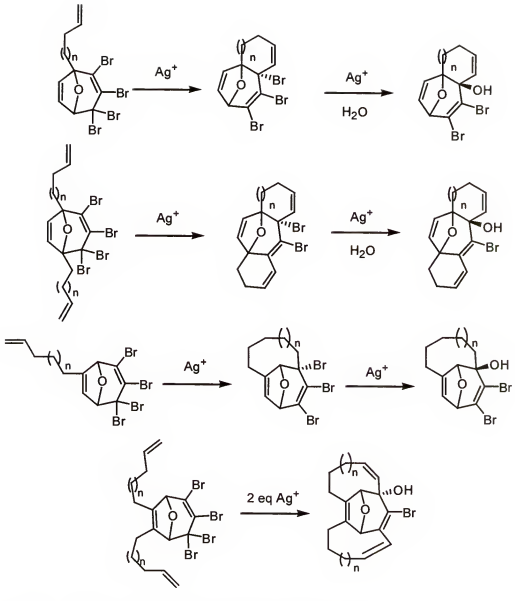
| Compd | Ar | Product (Yield %) |
|---|---|---|
| **103a** | Phenyl | **116c** (80%) |
| **103a** | 4-Methoxyphenyl | **111d** |
| **103a** | 3-Methoxyphenyl | **119a** |
| **103a** | 2-Methoxyphenyl | **119b** |
| **103a** | 1-Naphthyl | **119c** |
| **103c** | 4-Methoxyphenyl | **111b** |
| **103c** | 3,4-dimethoxyphenyl | **111c** |
| **103c** | 1-Naphthyl | **119d** |

Thus, Suzuki couplings provide an excellent alternative towards functionalizing the β carbon of **103**. The products were designated as containing the aryl group at the β position, because the spectral data of the phenyl boronic acid product matches with the phenyl cuprate addition product.

**Silver Mediated Intramolecular Cyclization of Tetrabromooxa[3.2.1]bicyclic Systems**

Having successfully explored the reactivity of the cations obtained from 2,3,4,4-Tetrabromo-8-oxa-bicyclo[3.2.1]octa-2,6-diene and related systems. We were interested in studying the feasibility of such reactions towards Intramolecular Cyclization. Intramolecular reactions are a powerful method that has been used in chemistry towards building carbon frameworks of natural products. Several interesting possibilities exist for studying intramolecular cyclizations of tetrabromo-8-oxa-bicyclo[3.2.1]octadienes (Note that the numbering for the bromines and dienes has been deliberately omitted as they will depend upon the substitution pattern of the molecule in concern) and are broadly outlined in Scheme 3.14. The starting materials for such cyclizations can be envisaged to originate from 2-substituted furans, 3-substituted furans, 2,5-disubstituted and 3,4-disubstituted furans. The diversity of such cyclizations, with regards to the possible products that can be obtained, can also be studied using primary alcohols in place of terminal alkenes. Such reactions ought to afford tricyclic polyethers in a one-pot process.

In addition, the terminal olefin could be an electron rich aromatic group, by analogy to the intermolecular reactions that have been reported in this work. A preliminary attempt was made to study such reactions where in such an intramolecular cyclization was explored towards the synthesis of the Colchicine.

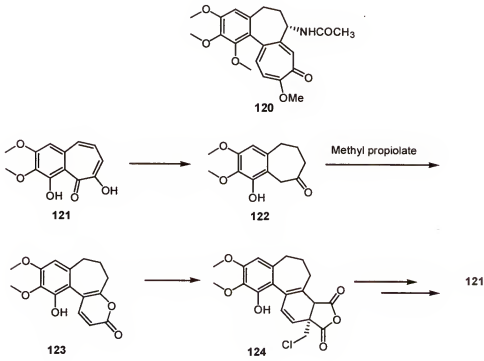



Scheme 3.14. Possible variants of intramolecular Cyclization.

Colchicine (**120**) is an alkaloid that was isolated from *Colchicum autumnale*. This alkaloid has a well-documented use in medicine. The total synthesis of this alkaloid was reported by Eschenmoser et al.[71] van Tamelen et al.[72] Nakamura et al.[73] Scott,[74] Woodward,[75] Martel et al.[76] Tobinaga et al.[77] Evans et al.[78] Boger et al.[79] and Cha et al.[80] A very brief review of the various routes used towards the total synthesis of this

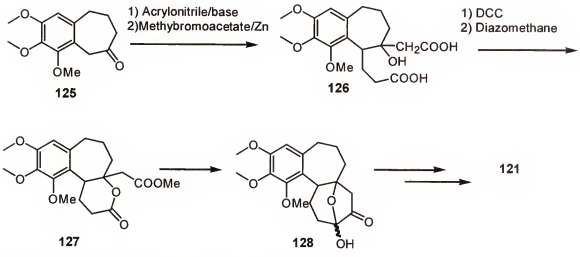
molecule, in chronological order, shall be presented followed by the used of tetrahalocyclopropenes towards the synthesis of this molecule.

Eschenmoser's synthesis starts out with the oxidation of pyrogallol to purpurogallin. Purpurogallin is methylated to afford dimethoxy-hydroxy-benzosuberone (**121**). The benzosuberone through a series of reductions is converted to the dimethoxy hydroxy cycloheptenone (**122**) that was condensed with methyl ester of propiolic acid in the presence of base to afford hydroxy pyrone (**123**). The key step towards setting up the C ring involved a Diels-Alder reaction (Scheme 3.15) of the hydroxy pyrone with α chloromethyl maleic anhydride to afford the tetracyclic **124**. The resulting compound (**124**) was converted to colchicine through a series of modifications.




Scheme 3.15. Eschenmoser's synthesis of Colchicine

The total synthesis reported by van Tamelen starts out with the trimethoxy benzocycloheptanone (**125**). Thus, **125** was treated with acrylonitrile in the presence of t-butoxide to 5(cyanoethyl)-2,3,4-trimethoxy-benzocyclo-6-heptanone (Scheme 3.16) that was subsequently treated with the organo zinc reagent obtained from methyl bromoacetate to afford **126**. The resulting compound were hydrolyzed to afford the hydroxy diacids that was converted to the desired lactone (**127**).

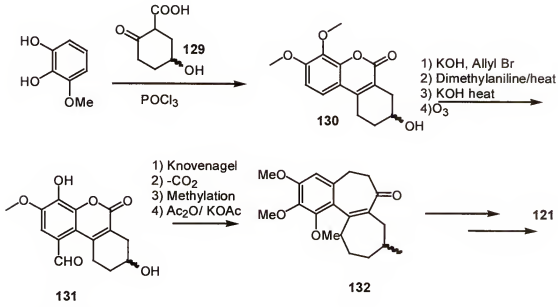



Scheme 3.16. van Tamelen's synthesis of Colchicine.

That was subsequently subjected to acyloin condensation to afford the complete colchicine skeleton (**128**). The compound **128** was subsequently converted to desacetamido colchicine that was converted to colchicine. Martel's synthesis is also similar in strategy however the disconnections that he uses towards making the C-ring are different.

Nakamura's synthesis involves the construction of the B ring of colchicine at a later stage of the synthesis and is outlined in Scheme 3.17. The synthesis starts with the condensation of O-methyl pyrogallol to **129**. The resulting coumarin (**130**) was subjected

to allylation and a Claisen rearrangement. The resulting compound was subjected to olefin rearrangement and ozonolyis to afford the highly substituted benzaldehyde (**131**). Compound **131** was subjected to Knovenagel condensation with malonic acid and decarboxylation and reduction to afford the coumarin **132**. The coumarin was subjected to hydrolysis, methylation, and cyclization to afford the complete carbon skeleton that was eventually converted to colchicine (**121**).

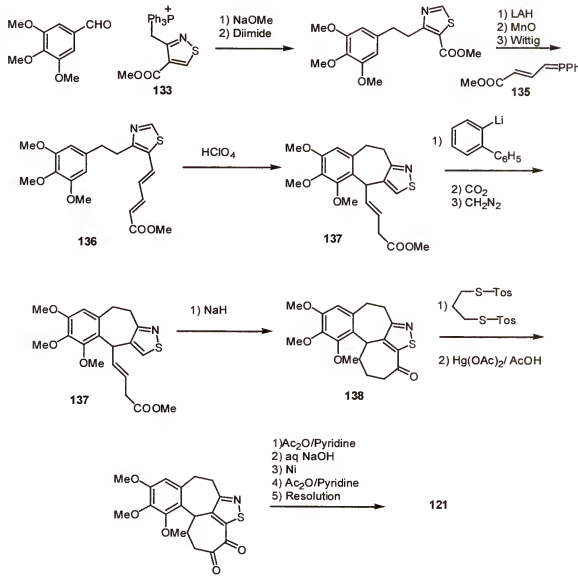



Scheme 3.17. Nakamura's synthesis of Colchicine

Historically, Woodward's synthesis of colchicine is of importance as he incorporates the amino functionality earlier on in the synthesis and then through a series of condensations forms the B and C rings. This avoids multiple reactions that are typically involved in incorporating the acetamido group towards the end of the synthesis.

Woodward's synthesis involves the incorporation of amino functionality as an isothiazole (**133**). Thus, isothiazole **133** is subjected to a Wittig reaction with 3,4,5-trimethoxy benzaldehyde; the resulting olefin is reduced using diimide to afford **134**.

The ester functionality on the isothiazole is then converted to an aldehyde that is subsequently subjected to another Wittig reaction with **135**. The resulting compound **136** is then subjected to acid catalyzed ring closure to afford **137** that contains the B ring.

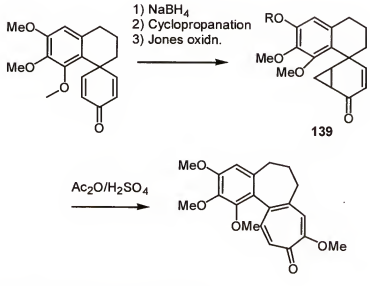



Scheme 3.18. Woodward's Synthesis of Colchicine

The remaining double bond in the side chain was reduced using diimide and a carboxyl group was appended on to the isothiazole ring. The resulting compound was subjected to an ester enolate, Dieckman, condensation to afford (**138**) that contains the C ring. The resulting compound through a series of steps converted to Colchicine as

shown in Scheme 3.18. The isothiazole group is removed at the end using Raney Ni reduction thus resulting in the free amino group.

Tobinaga's reported an elegant synthesis of colchicine that involved an acid catalyzed intramolecular rearrangement of a spirodienone (**139**). This route was based on the hypothetical biosynthesis of the alkaloid as suggested by Robinson. The general strategy is shown in Scheme 3.19. The starting material is made easily from its acyclic precursors by radical cyclization.

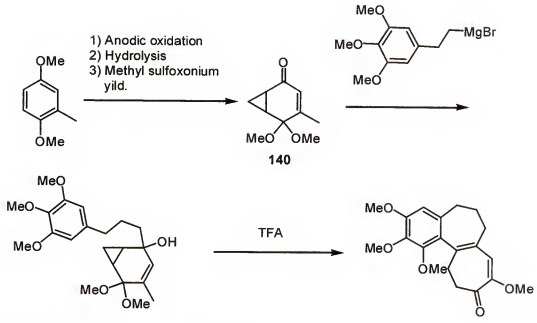



Scheme 3.19. Tobinaga's synthesis of Colchicine

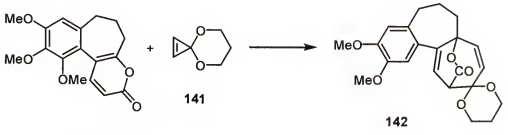
A similar synthesis was reported by Evan's where the tropolone equivalent was obtained from a bicyclo[4.1.0]hexanone (**140**). The overall synthetic scheme is shown in Scheme 3.20.

Boger's synthesis involves a [4+2] cycloaddition of cyclopropene ketal (**141**) to Eschenmoser's pyrone Scheme (3.21). The resulting cycloadducts (**142**) subjected to thermal decarboxylation of afford the complete skeleton of colchicine.

Cha's synthesis involves the use of an alpha methoxy substituted oxyallyl [4+3] cycloaddition.



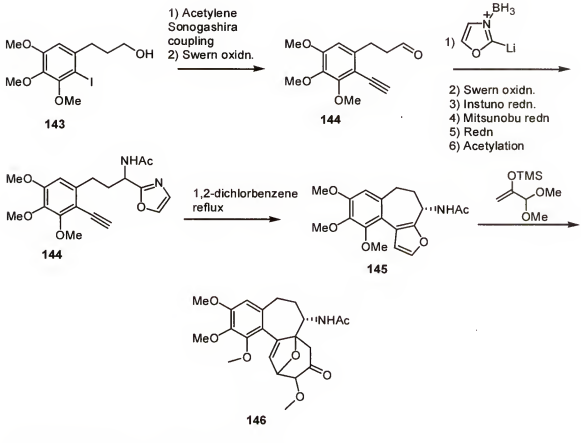

Scheme 3.20. Evan's synthesis of colchicine.




Scheme 3.21. Boger's synthesis of Colchicine

The synthesis involved the conversion of aryl iodide **143** to the acetylene by Sonogashira coupling. The alcohol was oxidized under Swern conditions to afford **144** that was then treated with the anion of oxazole, prepared in situ from the oxazole-borane complex. The resulting secondary alcohol was oxidized to the corresponding ketone enantioselectively reduced to the amine that was subsequently protected to afford the key

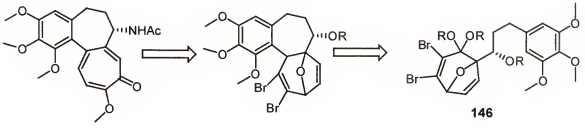
intermediate **144**. **144** was then subjected to a thermal intramolecular [4+2] cyclo-addition that resulted in the formation of the 2,3 substituted furan **145**. The resulting furan was subjected to a [4+3] cycloaddition to afford the desired [3.2.1]oxabicyclic system **146** that was subjected to mild hydrolysis to afford colchicine (Scheme 3.22). Other than Woodward's synthesis Cha's synthesis is the only one to date where the required amino functionality is established earlier on in the synthesis and thus avoids the extra steps involved in making the complete molecule.




Scheme3.22. Cha's synthesis of colchicine.

The retrosynthetic strategy that is based on tetrabromocyclopropene chemistry is give outlined in Scheme 3.23. The idea is based on the ability of tetrabromo oxabicyclic

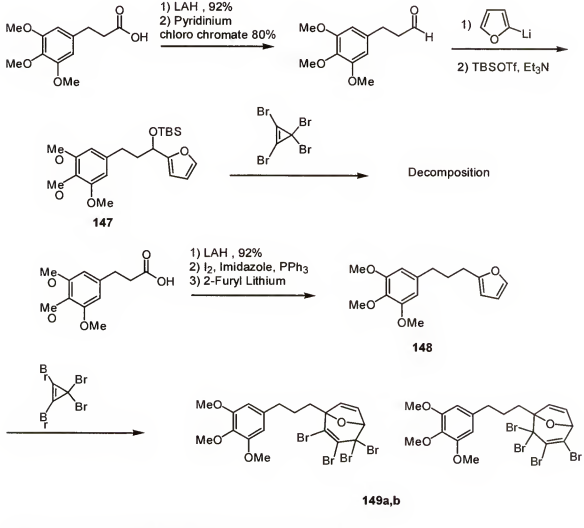
systems to take part in cationic additions with activated aromatic rings. Thus if one were to append the oxabicyclic system to the aromatic ring through a carbon chain, in this case three carbons being necessary, then such an intramolecular cyclization ought to lead to the desired colchicine skeleton. The initial set of reactions were straight forward and consisted of the addition 2-furyl lithium to 3,4,5-trimethoxyphenyl propanol that was obtained by a two step reduction, oxidation protocol. The resulting alcohol was protected in situ with TBSOTf. The resulting compound (**147**) in hand the [4+2] addition with tetrabromocyclopropene was attempted.




Scheme 3.23. Suggested retrosynthesis via tetrabromocyclopropene chemistry

The reaction did not give us the desired cycloadducts but instead decomposition was observed. In order to understand the compatibility of tetrabromocyclopropene with oxygen containing furans (an issue that has never been addressed before) a simple test reaction was performed using the TBS protected furfuryl alcohol. The reaction did not give us the desired cycloadducts and instead severe decomposition was observed. Similar such observations were made when the acetamide of furfuryl amine was used a partner in cycloaddition reaction with tetrabromocyclopropene. In order to avoid this complication a further simplification of the model system was done by removing the alcohol α to the furan, as shown in Scheme 3.24. When the Diels-Alder reaction was

carried out with **148** and tetrabromo-cyclopropene in refluxing benzene we were pleasantly surprised to obtain an 80% yield of the desired cycloadducts **149a,b** as a 1:1 regiomeric mixture (with regards to the placement of the geminal dibromo group with respect to the alkyl group on the bicyclic compound). The two compounds weren't separated and used as such in the next reaction. The intramolecular cycloaddition was carried out in the presence of Silver tetrafluoroborate and Silver oxide and in the presence of just Silver tetrafluoroborate.




Scheme 3.24. Study regarding Intramolecular cyclization

## Conclusions and Future Work

The addition of perhalocyclopropenes to cyclic dienes such as furan and cyclopentadiene provides a direct route to highly functionalized bicyclo[3.2.1]octene derivatives. There is interest in the application of these bridged synthons to natural product synthesis and as such, the scope and limitations of functionalizing the bridged adducts has been established. It was found that direct formation of cations promoted by silver ion are susceptible to attack by some nucleophiles, notable being the addition of electron rich aromatics. A more extensive family of nucleophiles can be substituted on these adducts by addition to the dihaloenones prepared by hydrolysis of the primary adducts. Hydride, Grignard and cuprate reagents all add efficiently to these enones to produce highly substituted compounds. Palladium catalyzed Suzuki couplings also occur very efficiently under mild conditions to afford β substituted products.

# CHAPTER 4
# EXPERIMENTAL

## General Procedures

All commercial reagents were used without further purification unless stated specifically in the procedures. Solvents, hexane and $CH_2Cl_2$, were distilled prior to use. Solvent mixtures used for chromatography are volume/volume mixtures. Dry THF and ether were prepared by distillation from sodium/ benzophenone under a nitrogen atmosphere prior to use. Reactions sensitive to air and moisture were performed under argon. Melting points of all compounds were measured using a Thomas-Hoover Capillary melting point apparatus. All melting points are uncorrected. Thin layer chromatography was performed using commercially available Silica Gel 60 $F_{254}$ (250μm thick). Flash chromatography was performed using Silica Gel using silica gel to crude material ratio of 30:1 or 20:1 depending on the nature of separation required. Analytical GC was performed using Shimadzu GCMS-QP5000, equipped with 5% phenyl column (30m, 0.25 mm ID, Restek Corp). IR spectra were recorded on a Perkin-Elmer IR spectrometer (4000-600 $cm^{-1}$). NMR was recorded using either Varian or Gemini spectrometers, in either $CDCl_3$ or Benzene-$d_6$ , that had operating frequency of 300 MHz for $^1H$ and 75 MHz for $^{13}C$ NMR. All chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane, all coupling constants (J) are in hertz. Elemental Analysis was performed by Atlantic Microlabs, Norcross, Georgia.

Tetrachlorocyclopropene and Tetrabromocyclopropene were synthesized as per the procedure described by Tobey et al. It must be mentioned that the initial batch of

tetrabromocyclopropene were prepared following the procedure outlined by Tobey. It was found that the product obtained contained significant amounts (about 20%) of monochloro tribromocyclopropene. These compounds were not separable by distillation. The resulting impurity carried over to the subsequent reactions. All the compounds synthesized using the impure tetrabromocyclopropene failed elemental analysis. The failures of crystalline compounds to pass elemental analysis lead us to go back and look at the synthesis of tetrabromocyclopropene. The use of 1.5 equivalents of boron tribromide resulted in the complete conversion of tetrachlorocyclopropene to tetrabromocyclopropene. The resulting product was purified by vacuum distillation. Therefore, an improved synthesis of tetrabromocyclopropene is outlined in the experimental section. All products obtained from subsequent reactions gave satisfactory elemental analysis. This substantiates the importance of elemental analysis as being a bench mark for not only the identity but also the purity of any compound.

**Synthesis of tetrabromocyclopropene**

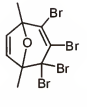
Tetrachlorocyclopropene 20g (0.112 mols) were taken neat in a 250 ml three-necked round bottom flask. A thermometer was inserted into the flask to monitor the internal temperature of the reaction mixture. A nitrogen line was attached through one neck and the flow of nitrogen was maintained at a steady rate to sweep out the resulting $BCl_3$. Boron tribromide (42.2 g , 0.168 mols Ventron Alfa, Beverly Ma.) was added to the tetrachlorocyclopropene dropwise. The internal temperature of the reaction mixture rises rapidly to about 40-60°C with the concomitant evolution of $BCl_3$. When all the Boron tribromide was added the resulting mixture was stirred for another hour during which the evolution of $BCl_3$ ceased. The crude tetrabromocyclopropene was then

distilled under reduced pressure 0.1 mm Hg. A 1mL forerun was discarded and pure tetrabromocyclopropene was obtained as a colorless liquid with a characteristic pungent odor (bp 60-62°C, 0.1 mm Hg). Two major fractions were collected the total mass of these fractions was about 37.1g (92 %). GC-MS analysis of this compound showed it to be greater than 97% purity. NOTE: Care should be taken during the vacuum distillation. The residual boron tribromide (bp 90°C, 760 mm Hg) escapes from the reaction mixture as a vapor during the distillation, and should be trapped using a Dewar (cooled in a mixture of dry ice and acetone). This is important as boron tribromide is corrosive and can potentially damage the vacuum pump. The numbering of the compounds is based on numbers assigned in Chapter 3.

**Typical Experimental Procedure for the Tetrabromocyclopropene Diels Alder Reactions.**

The reactions for the synthesis of **102a, 102b, 102c** and **102d** were performed as per the procedure outlined by Tobey and Law[5] and purified by column chromatography.

**2,3,4,4-Tetrabromo-1,5-dimethyl-8-oxa-bicyclo[3.2.1]octa-2,6-diene (102b)**




This compound was prepared by refluxing 2,5 dimethyl furan (1.62 g, 0.017 mols) with tetrabromocyclopropene (5.0 g, 0.014 mols) in benzene till all the starting materials were converted to the product. The benzene is removed under reduced pressure and the crude brown oil was purified by chromatography on a silica gel column using 10% ethyl

acetate in hexane. The product was obtained as a crystalline solid 5.3g (81 %). mp 65.0-69.0°C.

$^{1}$H NMR (300 MHz, $CDCl_3$) δ 6.50 (d, J= 5.5 Hz, 1H), 6.25 (d, J= 5.5 Hz, 1H), 1.93 (s, 3H), 1.68 (s, 3H).

$^{13}$C NMR (75 MHz, $CDCl_3$) δ 141.10, 135.5, 133.1, 128.5, 93.2, 89.5, 71.1, 23.9, 22.1. IR (NaCl) $cm^{-1}$2985, 2935, 1564, 1444, 1377, 1306, 1159, 1090, 942, 869, 758, 726, 714.

An analytically pure sample was obtained by sublimation. Anal. Calcd for $C_9H_8Br_4O$: C, 23.93; H, 1.78. Found C, 24.35; H, 1.75.

**General experimental procedure for the synthesis of ketones using aqueous Silver Nitrate**

**Method A**: The 2,3,4,4-Tetrabromo-dienes (**103a-c**) were dissolved in 10 mL of 50% aqueous acetone. The resulting solution was then treated with 2 equivalents of silver nitrate and the resulting mixture was stirred at room temperature. The mixture turns cloudy over a period of 45 min to 1 hour. The reaction was monitored by TLC until the entire starting tetrabromo compound was consumed. The reaction mixture was then treated with sufficient solid sodium bicarbonate (added in portions) to quench the nitric acid. The mixture was then filtered through celite to remove the insoluble silver salts and concentrated to remove the acetone. The resulting aqueous layer was then extracted thrice with 10 mLs of ethyl acetate. The organic layer was washed with water and concentrated to dryness. The product was purified further by column chromatography on silica using 5% Ethyl acetate in hexanes to obtain the corresponding ketones.

**Method B:** The hydrolysis of the tetrachloroadducts (200mg) was carried out in 10mL of 50% aqueous dioxane using one equivalent of silver nitrate and one equivalent of silver oxide. The reaction mixture was heated to a gentle reflux and monitored by tlc until all the starting material was converted to the product (**103d,e**). The solid silver salts were removed by filtration through celite. The dioxane layer was diluted with 20mL of water and extracted thrice with 10mL of ethyl acetate. The resulting organic layer was dried over anhydrous sodium sulfate and concentrated to dryness. The crude ketone was further purified by column chroma-tography over silica gel using 5% Ethyl acetate in hexanes.

**3,4-Dibromo-8-oxa-bicyclo[3.2.1]octa-3,6-dien-2-one (103a)**

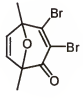
200 mg of **102a** upon hydrolysis and work up yield 112 mg of 5a (83 %) as pale yellow crystals. mp 86-87°C.

$^1$H NMR (300 MHz, $CDCl_3$) δ 7.02 (dd, J= 5.7Hz, 1.75H), 6.58 (dd, J= 5.7 Hz, 2.0 Hz, 1H), 5.39 (d, J = 1.75Hz, 1H), 5.17 (d, J = 2.0 Hz).

$^{13}$C NMR (75 MHz, $CDCl_3$) δ 183.8, 149.4, 138.9, 131.5, 120.3, 87.1, 86.9. IR (film on NaCl) $cm^{-1}$ 3096, 2983, 1704 (very strong), 1558, 1181, 1038, 927, 762, 695, 629, 550.

HRMS eI: Calculated $M^+$ for $C_7H_4Br_2O_2$ 278.8656. Found 278.8701. An analytically pure sample was obtained by sublimation. Anal. Calcd for $C_7H_4Br_2O_2$ : C 30.04, H 1.44. Found C 30.07, H 1.32.

**3,4-Dibromo-1, 5-dimethyl-8-oxa-bicyclo[3.2.1]octa-3,6-dien-2-one (103b)**




350 mg of **102b** upon hydrolysis with 290 mg of silver nitrate followed by work up and column chromatography on silica gel using 5% ethyl acetate in hexanes gave 200.9 mg (85%) of **103b** as a colorless semi solid that slowly crystallized upon standing. mp 57.0-58.0°C.

$^1$H-NMR (300 MHz, $CDCl_3$) δ 6.70 (d, J = 5.4 Hz, 1H), 6.20 (d, J = 5.4 Hz, 1H), 1.80 (s, 3H), 1.60 (s, 3H).

$^{13}$C-NMR (75 MHz, $CDCl_3$) δ 186.2, 154.5, 142.5, 135.3, 120.9, 93.0, 91.7, 23.0, 17.9. IR (film on NaCl) $cm^{-1}$ 2987, 2936, 1708 (very strong), 1551, 1376, 1182, 1164, 1120, 942, 878, 730.

HRMS eI: Calculated $M^+$ for $C_9H_8Br_2O_2$ 226.9707. Found 226.9719. An analytically pure sample was obtained by sublimation. Anal. Calcd for $C_9H_8Br_2O_2$ : C 35.10, H 2.62. Found C 35.14, H 2.62.

**3,4-Dibromo-bicyclo[3.2.1]octa-3,6-dien-2-one (103c)**

0.5g of **102c** upon hydrolysis, workup and column chromatography on silica gel using 5% ethyl acetate gave 300 mg (90%) of **103c** as a white crystalline solid. mp 79-81°C.

$^1$H NMR (300 MHz, $CDCl_3$) δ 6.84 (dd, J=4.9, 2.9 Hz, 1H), 6.32 (dd, J= 4.9, 3.6 Hz, 1H), 3.80 (dd, J=4.67, 3.6 Hz, 1H), 3.65(m, 1H), 2.72 (d, J = 10.8 Hz, 1H), 2.46 (ddd, J= 10.8, 4.68, 4.67 Hz, 1H).

$^{13}$C NMR ($CDCl_3$, 75 MHz) δ 188.5, 153.5, 141.7, 133.6, 121.4, 56.0, 55.5, 50.3. IR (NaCl ) cm$^{-1}$ 2973, 2945, 1694(very strong), 1557, 1237, 1212, 1127, 1033, 924, 766, 708.

HRMS el Calculated $M^+$ for $C_8H_6Br_2O$ 275.8785. Found 275.8787. An analytically pure sample was obtained by sublimation. Anal. Calcd for $C_8H_6Br_2O$: C 34.57, H 2.18. Found C 34.68, H 2.07.

**3,4-Dichloro-8-oxa-bicyclo[3.2.1]octa-3,6-dien-2-one(103d)**

200mg of (**102d**) was dissolved in 10mL of 50% aqueous dioxane and heated to 90°C with 0.139g of silver nitrate and 0.202 g of silver oxide. The reaction mixture was worked up as described above to yield 130mg (83.7%) of **103d** as a colorless crystalline solid. mp 75-76°C.

$^1$H NMR (300 MHz, $CDCl_3$) δ 7.00 (dd, J= 1.9, 5.7 Hz, 1H), 6.60(dd, J= 2.4, 5.7 Hz, 1H), 5.30 (d, J=1.9 Hz, 1H), 5.16 (d, J=1.9 Hz, 1H). $^{13}$C NMR ($CDCl_3$, 75 MHz) 184.5, 153.6, 138.8, 131.7, 123.9, 87.1, 85.1. IR (NaCl) cm$^{-1}$ 3098, 1713, 1575, 1197, 1059, 928, 885, 771, 702, 640.

**3,4-Dichloro-bicyclo[3.2.1]octa-3,6-dien-2-one(103e)**

200mg of 102e was dissolved in 10mL of 50% aqueous dioxane and heated to 90°C with 0.139g of silver nitrate and 0.202 g of silver oxide. The reaction mixture was worked up as described above to yield 132 mg (85.7%) of 103e as colorless oil.

$^1$H NMR (300 MHz, $CDCl_3$) δ 6.82 (dd, J=5.23, 3.0 Hz, 1H), 6.31(dd, J=5.23, 3.3 Hz, 1H), 3.63 (m, 2H), 1.08(m, 1H), 2.50(ddd, 1H).

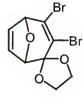
$^{13}$C NMR ($CDCl_3$, 75 MHz) δ189.1, 157.7, 141.6, 133.8, 124.5, 56.3, 52.7, 50.1. IR (NaCl) cm$^{-1}$ 2975, 1699, 1572, 1226, 1134, 1052, 770.

HRMS Calculated Exact Mass for $C_8H_6Cl_2O$: 187.9796. Found

Analysis calculated for $C_8H_6Cl_2O$ C, 50.83; H, 3.20. Found C, 50.91; H, 3.28.

**Method C:** In a glove box, silver tetrafluoroborate (2 equivalents) was weighed and transferred into a 10 mL round bottom flask containing a magnetic stir bar. The flask was then charged with dry ethylene glycol (2 equivalents). The reaction mixture was cooled to -78°C. In a dry vial, 1 equivalent of **102a** was dissolved in about 1.5 mL of dry methylene chloride. The solution of **102a** was then added drop wise with stirring into the flask containing silver tetrafluoroborate and ethylene glycol. The reaction mixture was stirred and allowed to warm up to room temperature. The reaction mixture was stirred at room temperature for 10 minutes and monitored by TLC. Upon complete consumption of the starting material, the reaction mixture was diluted with 10 mL of methylene chloride and quenched with 5 mL of saturated sodium bicarbonate. The silver bromide was filtered through a sintered glass filter. The organic layer was washed with water dried over anhydrous sodium sulfate and concentrated to remove the solvent. The residue was subjected to column chromatography using 15% ethyl acetate and 5% triethylamine in hexanes or alternatively passed through a plug of basic alumina.

**Spiro[3,4-Dibromo-8-oxabicyclo[3.2.1]octa-3,6-diene-[2,2']dioxolane] (104a)**

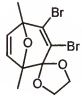



100 mg of **102a** was dissolved in about 1.5 mL of dry methylene chloride and added dropwise to a mixture of 59 mg of dry ethylene glycol and 91.8 mg of silver tetrafluoroborate in about 1.0 mL of dry dichloromethane. The reaction was worked up

as given in the typical procedure to obtain 65.5mg (86%) of **104a** was obtained as colorless semi solid that crystallizes over a period of time. mp 106-108°C.

$^1$H-NMR (300 MHz $CDCl_3$ δ 6.92 (dd, J = 5.9 Hz, 1.3 Hz, 1H), 6.34, (dd, J = 5.9 Hz, 1.3 Hz 1H), 4.98 (d, J= 1.3 Hz, 1H), 4.82 (d, J= 1.3 Hz, 1H), 4.40-4.00 (m, 4H); $^{13}$C-NMR (75 MHz, $CDCl_3$) δ 140.2, 133.6, 131.3, 123.0, 104.7, 84.6, 84.5, 67.2, 65.5; IR (NaCl) cm$^{-1}$ 2900, 2895, 1290, 1152, 1067, 1009, 949, 927, 720; HRMS CI: Calculated $M^+$+H for $C_9H_8Br_{81}BrO_3$ 324.8947. Found 324.8923. An analytical sample was obtained by recrystalizing the compound from 20% ether in pentanes. Analysis Calculated for $C_9H_8Br_2O_3$ C, 33.37; H, 2.49. Found C, 33.37; H, 2.49.

**Spiro[3,4-Dibromo-1,5-dimethyl-8-oxabicyclo[3.2.1]octa-3,6-diene-[2,2']dioxolane] (104b)**




Reaction of 100mg of **102b** with 95 mg of silver tetrafluoroborate and 55 mg of ethylene glycol followed by work up and column chromatography yields 68 mg (87 %) of **104b** as a semi solid.

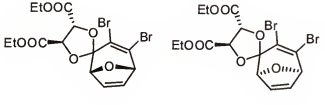
$^1$H-NMR (300 MHz $C_6D_6$) δ 6.14 (d J= 5.6 Hz, 1H), 5.88 (d J= 5.6 Hz, 1H), 3.95-3.34 (m, 4H), 1.46 (s, 3H), 1.36 (s, 3H); $^{13}$C-NMR (75 MHz, $C_6D_6$) δ 143.1, 138.5, 136.3 126.8, 108.2, 91.3, 89.8, 67.24, 67.15, 22.7, 17.9; IR (NaCl) cm-1 2983, 2936, 2900, 1587, 1447, 1380, 1205, 1162, 1141, 1118, 1045, 1005, 952, 878, 734. HRMS CI: Calculated $M^+$+H for $C_{11}H_{12}Br_2O_3$ 350.9231. Found 350.9194. Analysis Calculated for $C_{11}H_{12}Br_2O_3$ C, 37.53; H, 3.44. Found C, 37.91; H, 3.35.

**Spiro[3,4-Dibromo-bicyclo[3.2.1]octa-3,6-diene-[2,2']dioxolane] (104c)**

Reaction of 100mg of **102c** with 101.0 mg of Silver tetrafluororate and 59.0 mg of dry ethylene glycol after workup and purification afforded 62.7 mg (82 %) of **104c** as colorless oil.

$^1$H-NMR (300 MHz $C_6D_6$) δ 6.33 (dd, J= 5.4 Hz, 2.8 Hz, 1H), 5.92 (dd, J= 5.3 Hz, 3.0 Hz, 1H), 3.90-3.30 (m, 4H), 2.93 (m, 1H), 2.65 (m, 1H), 2.25 (d, J= 10.63 Hz, 1H), 1.65 (m, 1H). $^{13}$C-NMR (75 MHz, $C_6D_6$ ) δ 142.5, 136.5, 134.0, 125.1, 109.1, 66.9, 65.6, 52.8, 50.9, 44.8. IR (NaCl) cm$^{-1}$ 2950, 2891.5, 1596.5, 1450.4, 1303.3, 1206.1, 1142.6, 1120.0, 1034.0, 1015.4, 964.1, 948.3, 922.1, 737.5. HRMS eI: Calculated $M^+$ for $C_{10}H_{10}Br_2O_2$ 319.9047. Found 319.9055. Analysis Calculated for $C_{10}H_{10}Br_2O_2$ C, 37.30; H, 3.13. C37.63; H, 3.03.

**Tartrate Ketals 105a,b**




In a dry flame dried flask, 1.02g of silver tetrafluoroborate was added. To this flask about 20 mL of dry dichloromethane and 0.55g of L-diethyl tartrate was added, the resulting mixture was stirred and cooled to -78°C. In about 20 mL of dry dichloromethane 1.0g of **102a** was dissolved and added dropwise to the cold silver tetrafluoroborate. The mixture was rapidly warmed to room temperature by removing the

acetone dry ice bath and monitored by tlc till all the starting material was consumed. The reaction mixture was quenched with cold saturated aqueous sodium bicarbonate and filtered through celite to remove all the silver salts. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was subjected to MPLC on silica column and the ketals 0.5g of (**105a** 45.2%) and 0.495 of (**105b** 45.0%) were eluted with 5% ethyl acetate in heptanes.

Spectral Data for **105a**: $^{1}$H-NMR (300 MHz $CDCl_3$) δ 6.96 (dd, J= 5.7, 1.9 Hz, 1H), 6.45(dd, J= 5.7, 2.1 Hz, 1H), 5.04 (d, J= 6.42 Hz, 1H), 4.98 (m, 2H), 4.79 (d, J= 6.42 Hz, 1H), 4.35-4.25 (m, 4H), 1.34 (t, J= 7.37, 6H). $^{13}$C-NMR (75 MHz $CDCl_3$) δ 169.2, 167.3, 140.2, 135.9, 131.5, 121.1, 108.0, 84.8, 84.6, 78.1, 77.8, 62.6, 62.5.14.31, 14.29. IR (NaCl $cm^{-1}$) 2982, 1746.8, 1606, 1373, 1224, 1147, 1037, 930, 724. HRMS Calculated for $C_{15}H_{16}Br_2O_7$ 466.9341. Found 466.9349. $[\alpha]_D$ = +3.39.

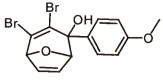
Spectral Data for **105b**: $^{1}$H-NMR (300 MHz $CDCl_3$) δ 6.92 (dd, J= 5.9, 1.7 Hz, 1H), 6.39 (dd, J= 5.9, 2.1 Hz, 1H), 5.16 (d, J= 2.1 Hz, 1H), 5.09 (d, J= 6.18 Hz, 1H), 4.97 (d, J= 1.7 Hz, 1H), 4.88 (d, J= 6.18 Hz, 4H), 4.36-4.24 (m, 4H) 1.32 (t, J= 7.37, 6H). $^{13}$C-NMR (75 MHz $CDCl_3$) δ 169.2, 167.3, 140.5, 135.5, 131.1, 121.3, 108.3, 84.9, 84.6, 78.9, 78.2, 62.64, 62.57, 14.33, 14.29. IR (NaCl $cm^{-1}$) 2982, 1746.8, 1606, 1373, 1224, 1147, 1037, 930, 724. HRMS Calculated for $C_{15}H_{16}Br_2O_7$ 466.9341. Found 466.9349. $[\alpha]_D$ = +4.58.

**General experimental procedure for arylation of oxabicyclo systems using Silver tetrafluoroborate.**

In a glove box, 183.7 mg (0.94 mmols) of dry silver tetrafluoroborate and 217.4 mg (0.94 mmols) of dry silver oxide were weighed and transferred into a 10 mL round

bottom flask containing a magnetic stir bar. This flask was then taken out of the glove box and kept under argon atmosphere. The contents of this flask were then charged with about 1ml of dry methylene chloride and 1.88 mmols of the desired aromatic compound. The contents to the flask were then cooled to -78°C. In a dry vial 200 mg (0.47 mmols) of 2,3,4,4-Tetrabromo-8-oxabicyclo[3.2.1]octa-2,6-diene (**102a**) was dissolved in 1.5 mL of dry methylene chloride. This solution was then added drop wise over a period of about 5-10 mins to the stirring mixture of silver tetrafluoroborate and silver oxide in the flask. The contents of the flask were kept at -78°C and stirred for another 1 hour and check by TLC to confirm the completion of the reaction. After all the starting material was consumed, the reaction mixture was quenched with 5 ml of sodium bicarbonate solution and extracted thrice with 15 mLs of ethyl acetate. The organic layer was washed with water, dried over anhydrous sodium sulfate, and concentrated to dryness. The residual organic material was subjected to column chromatography over silica gel using a gradient of hexanes to 5% Ethyl acetate in hexanes.

**3,4-Dibromo-2- (4-methoxy-phenyl)-8-oxa-bicyclo[3.2.1]octa-3,6-dien-2-ol (106a)**



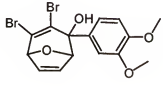

200 mg of **102a** affords after work and column chromatography with 5% ethyl acetate in hexanes 126 mg (87 %) of **106a** as colorless crystals. mp 109-111 ° C.

$^1$H-NMR (300 MHz $CDCl_3$) δ 7.18 (d, J= 8.4 Hz, 2H), 6.88 (d, J= 8.4 Hz, 2H), 6.82 (dd, J= 6.2, 1.2 Hz, 1H), 5.80 (dd, J= 6.2, 1.2Hz, 1H), 5.00 (d, J=1.2 Hz, 1H), 4.89 (d, J=1.2 Hz, 1H), 3.80 (s, 3H), 3.20 (br s, 1H).

$^{13}$C-NMR (75 MHz, $CDCl_3$) δ 159.7, 137.8, 131.1, 130.9, 129.2, 127.8, 113.8, 111.5, 88.7, 84.5, 78.8, 55.5. IR (NaCl) $cm^{-1}$: 3446 (br), 2958, 1512, 1301, 1249, 1174, 1032, 907, 835, 734, 714.

HRMS Calculated $M^+$ for $C_{14}H_{12}{}^{81}BrBrO_3$. 387.91343. Found 387.9133. An analytically pure sample was obtained by recrystalizing the compound from 10% ethyl acetate in hexanes. Anal. Calcd for $C_{14}H_{12}Br_2O_3$ : C 43.33, H 3.12. Found C 43.09, H 3.08.

**3,4-Dibromo-2-(3,4-dimethoxy-phenyl)-8-oxa-bicyclo[3.2.1]octa-3,6-dien-2-ol (106b)**



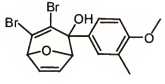

200mg of **102a** upon reaction followed by workup and column chromatography on silica gel with 5% ethyl acetate afforded 134.7 mg (75%) of **106b** as pale cream crystals. mp 139-140°C.

$^1$H-NMR (300 MHz, $CDCl_3$) δ 6.90-6.68 (m, 4H), 5.83 (dd, J= 5.8, 1.75 Hz, 1H), 5.02 (d, J=1.75 Hz, 1H), 4.90 (d, J=1.76 Hz, 1H), 3.90 (s, 6H), 3.31 (br s, 1H).

$^{13}$C-NMR (75 MHz, $CDCl_3$) δ 149.0, 137.6, 131.2, 130.9, 129.5, 128.2, 119.1, 110.9, 109.7, 88.7, 84.5, 78.8, 56.2, 56.1. IR (neat on NaCl plate) $cm^{-1}$ 3446(br), 2958, 2935, 1601, 1515, 1463, 1415, 1261, 1142, 1029, 918, 860, 730.

HRMS Calculated $M^+$ for $C_{15}H_{14}Br_2O_4$: 415.9259. Found 415.9278. An analytically pure sample was obtained by recrystalizing the compound from 10% ethyl acetate in hexanes. Anal. Calcd for $C_{15}H_{14}Br_2O_4$: C 43.09, H 3.38. Found C 43.24, 3.39.

**3,4-Dibromo-2- (4-methoxy-3-methyl-phenyl)-8-oxa-bicyclo[3.2.1]octa-3,6-dien-2-ol (106c)**



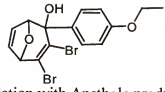

200 mg of **102a** affords after reaction and purification by column chromatography on silica gel with 5% ethyl acetate 132.7 mg (70%) of **106c**. mp 115-117°C.

$^1$H-NMR (300 MHz, $CDCl_3$) δ 7.04 (s, 1H), 7.02 (d, J = 8.5 Hz, 1H), 6.82 (dd, J= 6.0, 1.75, Hz, 1H), 6.78 (d, J= 8.5 Hz, 1H), 5.83 (dd, J = 6.0 , 1.75 Hz, 1H), 5.05 (d, J=1.75 Hz, 1H), 4.88 (d, J= 1.75 Hz, 1H), 3.82 (s, 3 H), 3.20 (br s, 1H), 2.22 (s, 3H).

$^{13}$C-NMR (75 MHz, $CDCl_3$) δ 157.8, 137.7, 131.2, 131.0, 128.7, 128.6, 126.8, 125.2, 109.6, 88.7, 84.5, 78.8, 55.5, 16.7. IR (NaCl ) $cm^{-1}$ 3436, 2956, 2835, 1503, 1251, 1132, 1032, 920, 734.

HRMS Calculated exact $M^+$ for $C_{15}H_{15}Br_2O_3$ 399.9309. Found 399.9356. An analytically pure sample was obtained by recrystalizing the compound from 10% ethyl acetate in hexanes. Anal. Calcd for $C_{15}H_{15}Br_2O_3$: C 44.81, H 3.51. Found C 44.54, H 3.50.

**3,4-Dibromo-2-(4-ethoxy-phenyl)-8-oxa-bicyclo[3.2.1]octa-3,6-dien-2-ol(106d)**



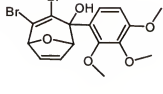

200 mg of **102a** upon arylation with Anethole produced 156 mg (82%) of **106d** as a colorless semi solid.

$^1$H-NMR (300 MHz, $CDCl_3$) δ 7.17(d, J= 8.8 Hz, 2H), 6.87 (d, J= 8.8 Hz, 2H), 6.84(dd, J= 1.9, 5.95 Hz, 1H), 5.82 (dd, J= 2.14, 5.95 Hz, 1H), 5.04 (d, J= 1.9 Hz), 4.90 (d, J=2.14 Hz, 1H), 4.08 (q, J= 7.13 Hz, 2H), 3.20(br s, 1H), 1.42 (t, J= 7.13 Hz, 3H).

$^{13}$C-NMR (75 MHz, $CDCl_3$) δ 159.1, 137.8, 131.0, 130.9, 129.0, 128.5, 127.8, 114.3, 88.7, 84.5, 78.8, 63.6, 15.0. IR (neat on NaCl plate) $cm^{-1}$3440, 2978, 1610, 1511, 1247, 1047, 907, 734, 601.

Anal. Calcd for $C_{15}H_{14}Br_2O_3$: C 44.81, H 3.61. Found C 45.05, H 3.61.

**3,4-Dibromo-2-(2,3,4-trimethoxy-phenyl)-8-oxa-bicyclo[3.2.1]octa-3,6-dien-2-ol (106e)**

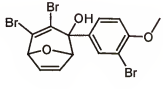



200mg of **102a** upon reaction followed by workup and column chromatography with 5% ethyl acetate afforded 155.5 mg of **106e** as pale cream crystals. Yield 73.3%. mp 112-114°C. [Note: The compound exhibits restricted rotation at the bond connecting the aryl ring and bicyclic system and as a result shows broad peaks at room temperature and therefore the NMR data is reported for the major rotamer at elevated temperature.]

$^1$H-NMR (300 MHz, $d_6$-DMSO, 115°C) δ 6.92 (d, J= 9.0 Hz, 1H), 6.64- 6.76 (m, 3H), 5.74 (d, J= 5.4 Hz, 1H), 5.00 (s, 1H), 4.88 (s, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.72 (s, 3H). $^{13}$C-NMR (75 MHz, $d_6$-DMSO, 115°C) δ 153.0, 150.7, 135.3, 130.9, 130.7, 128.4, 123.4, 122.2, 106.7, 87.3, 83.0, 76.9, 60.3, 59.6, 55.5. IR (NaCl) cm$^{-1}$ 3449 (br), 2942, 2838, 1599, 1494, 1464, 1413, 1298, 1278, 1234, 1101, 1049, 923, 730.

HRMS Calculated exact $M^+$ for $C_{16}H_{16}Br_2O_5$ 445.9364. Found 445.9366. An analytically pure sample was obtained by recrystalizing the compound from 20% ether in pentanes. Anal. Calcd for $C_{16}H_{16}Br_2O_5$: C 42.89, H 3.60. Found C 43.17, H 3.61.

**3,4-Dibromo-2- (3-Bromo-4-methoxy-phenyl)-8-oxa-bicyclo[3.2.1]octa-3,6-dien-2-ol (106f)**



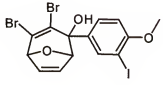

200 mg of **102a** upon arylation with *o*-Bromoanisole produced 176 mg (80.0%) of **106g** as a colorless amorphous solid. The hydrolysis compound **5a** was also isolated 85 mg (65 %) during column chromatography. mp 90-92ºC.

$^1$H-NMR (300 MHz, $CDCl_3$) δ 7.56 (d, J= 1.9 Hz, 1H), 7.15(dd, J= 1.9, 8.55 Hz, 1H), 6.86 (m, 2H), 5.85 (dd, J= 2.0, 5.8 Hz, 1H), 5.05 (d, J= 1.9 Hz, 1H), 4.88(d, J= 2.1 Hz, 1H), 3.90(s, 3H), 3.36(br s, 1H).

$^{13}$C-NMR (75 MHz, $CDCl_3$) δ 155.9, 138.3, 131.6, 131.5, 130.7, 130.6, 127.7, 127.0, 111.8, 111.6, 88.6, 84.5, 56.5. IR (NaCl) An analytically pure sample was obtained by recrystalizing the compound from 20% ether in pentanes.

Anal. Calcd for $C_{14}H_{11}Br_3O_3$: C 36.02, H 2.37. Found C 36.28, H 2.38.

**3,4-Dibromo-2- (3-iodo-4-methoxy-phenyl)-8-oxa-bicyclo[3.2.1]octa-3,6-dien-2-ol (106g)**



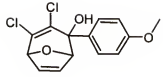

200 mg of **102a** upon arylation with *o*-Iodoanisole produced 77 mg (32%) of **106f** as a colorless amorphous solid. The hydrolysis compound **5a** was also isolated 85 mg (65 %) during column chromatography. mp 164-165°C.

$^1$H-NMR (300 MHz, $CDCl_3$) δ, 7.75 (s, 1H), 7.14 (d, J= 8.6 Hz, 1H), 6.86 (d, J = 5.7 Hz, 1H), 6.78 (d, J= 8.6 Hz, 1H), 5.85 (dd, J= 5.7, 1.66 Hz, 1H), 5.05 (d, J=1.66Hz, 1H), 4.88 (s, 1H), 3.90 (s, 3H), 3.28 (br s, 1H).

$^{13}$C-NMR (75 MHz, $CDCl_3$) δ 158.2, 138.3, 137.52, 131.6, 131.2, 130.6, 130.2, 128.1, 127.7, 110.5, 88.6, 86.0, 84.5, 56.6. IR (NaCl) cm$^{-1}$ 3430 (br), 2961, 1598, 1556, 1490, 1253, 1050, 913, 730, 667.

An analytically pure sample was obtained by recrystalizing the compound from 20% ether in pentanes. Anal. Calcd for $C_{14}H_{11}Br_2IO_3$: C 32.72, H 2.16. Found C 32.94, H 2.27.

**3,4-Dichloro-2-(4-methoxy-phenyl)-8-oxa-bicyclo[3.2.1]octa-3,6-dien-2-ol (106h)**



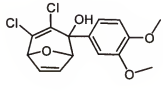

200 mg of **102d** upon arylation with anisole, followed by work up and column chromatography afforded 157 mg (68%) of **106h** as a colorless amorphous solid. mp 130-132°C.

$^1$H-NMR (300 MHz, $CDCl_3$) δ 7.18 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 6.78 (dd, J= 5.8, 1.5 Hz, 1H), 5.80 (dd, J = 5.8, 2.0 Hz, 1H), 4.94 (d, J= 1.5 Hz, 1H), 4.85 (d, J= 2.0 Hz, 1H), 3.80 (s, 3H), 3.40 (br s, 1H).

$^{13}$C-NMR (75 MHz, $CDCl_3$) δ 159.6, 137.8, 136.9, 130.9, 128.2, 127.9, 121.2, 113.9, 89.2, 82.4, 82.1, 55.4. IR (NaCl) $cm^{-1}$ 3449 (br), 2961, 2837, 1611, 1513, 1250, 1176.5, 1041, 910, 760, 735, 719, 649, 630.

HRMS EI Calculated Exact Mass for $C_{14}H_{12}Cl_2O_3$ : 298.0163. Found 298.0110. An analytically pure sample was obtained by recrystalizing the compound from 20% ethyl acetate in hexanes. Anal. Calcd for $C_{14}H_{12}Cl_2O_3$: C 56.21, H 4.04. Found C 56.14, H 4.05.

**3,4-Dichloro-2-(3,4-methoxy-phenyl)-8-oxa-bicyclo[3.2.1]octa-3,6-dien-2-ol (106i)**



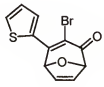
200 mg of **102d** upon arylation with veratrole, followed by work up and column chromatography afforded 172 mg (64%) of **106i** as a colorless amorphous solid. mp 151-152ºC.

$^1$H-NMR (300 MHz, $CDCl_3$) δ 6.90 (d, J = 1.76, 1H), 6.83 (d, J = 8.2, 1H), 6.77 (dd, J = 6.0, 1.5 Hz, 1H), 6.71 (dd, J = 8.2, 1.76 Hz, 1H), 5.82 (dd, J = 6.0, 2.0 Hz, 1H), 4.95 (d, J = 1.5, 1H), 4.87 (d, J = 2.0, 1H).

$^{13}$C-NMR (75 MHz, $CDCl_3$) δ 149.0, 137.7, 137.0, 130.9, 130.6, 128.5, 119.2, 110.9, 109.8, 89.18, 82.5, 56.1, 56.0. IR( NaCl ) $cm^{-1}$ 3452 (br), 2959, 2935, 2837, 1611, 1514, 1416, 1236, 1144, 1028, 877, 758, 734.

HRMS EI Calculated Exact Mass for $C_{15}H_{14}Cl_2O_4$ 328.0269. Found 328.0278. An analytically pure sample was obtained by recrystalizing the compound from 20% ethyl acetate in hexanes. Anal. Calcd for $C_{15}H_{14}Cl_2O_4$: C 54.73, H 4.29. Found C 54.94, H 4.27.

**3-Bromo-4-thiophen-2-yl-8-oxa-bicyclo[3.2.1]octa-3,6-dien-2-one (111a)**

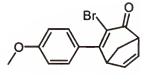



200 mg of **102a** upon arylation with thiophene produced 105 mg (79%) of **111a** as pale brown semi solid.

$^1$H-NMR (300 MHz, $CDCl_3$) δ, 7.76 (d, J= 5.26 Hz, 1H), 7.72 (d, J= 3.8 Hz, 1H), 7.26 (dd, J= 5.0, 3.8 Hz, 1H), 6.94 (dd, J= 5.55, 1.46, Hz, 1H), 6.60 (dd, J= 5.55, 2.00 Hz, 1H), 5.88 (d, J= 1.76 Hz, 1H), 5.22 (d, J= 2.00 Hz, 1H).

$^{13}$C-NMR (75 MHz, $CDCl_3$) δ 185.7, 151.8, 138.8, 136.3, 132.9, 131.6, 131.4, 128.0, 112.1, 86.7, 84.0. IR (neat on NaCl plate) $cm^{-1}$ 3100, 1689(very strong), 1544, 1416, 1254, 1175, 1068, 935, 715, 699. HRMS EI:Calculated exact $M^+$ $C_{11}H_7BrO_2S$ is 281.9350. Found 281.9353.

**3-Bromo-4- (4-methoxy-phenyl)-bicyclo[3.2.1]octa-3,6-dien-2-one (111b)**




200 mg of **102d** upon arylation with anisole followed by work up and column chromatography afforded 110 mg (77%) of **111b** as a colorless amorphous solid. mp 131-132°C

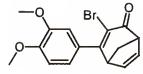
$^1$H-NMR (300 MHz, $CDCl_3$) δ 7.45 (d, J = 8.7 Hz, 2H), 6.96 (d, J = 8.7 Hz, 2H), 6.80 (m, 1H), 6.32, (m 1H), 3.86 (s, 3H), 3.66 (m, 2H), 2.72 (d, J= 10.35 Hz, 1H), 2.48-2.58 (m, 1H).

$^{13}$C-NMR (75 MHz, $CDCl_3$) δ 191.2, 163.9, 160.5, 142.9, 133.2, 131.0, 129.5, 115.6, 113.8, 56.2, 55.5, 51.7, 50.2. IR (NaCl) $cm^{-1}$ 2966, 2838, 1683(very strong), 1604, 1507, 1250, 1178, 1027, 832, 773, 713.

HRMS Calculated exact $M^+$ for $C_{15}H_{13}BrO_2$ 304.0099. Found 304.0094.

Anal. Calculated for $C_{15}H_{13}BrO_2$: C, 59.04; H, 4.29. Found C 58.90; H 4.29.

**3-Bromo-4-(3,4-dimethoxy-phenyl)-bicyclo[3.2.1]octa-3,6-dien-2-one (111c)**



200 mg of **102d** upon arylation with veratrole followed by work up and column chromatography afforded 107 mg (67%) of **111c** as a colorless amorphous solid. mp 117-119°C.

$^1$H-NMR (300 MHz, $CDCl_3$) δ 7.06 (s, 1H), 7.04 (d, J = 8.8 Hz, 1H), 6.92 (d, J = 8.8 Hz, 1H), 6.82 (m, 1H), 6.34 (m, 1H), 3.94 (s, 3H), 3.92 (s, 3H) 3.70-3.64 (m, 2H), 2.74 (d, J = 10.35 Hz, 1H), 2.60-2.50 (m, 1H).

$^{13}$C-NMR (75 MHz, $CDCl_3$) δ 191.1, 163.9, 150.0, 148.5, 142.8, 133.2, 131.2, 120.9, 115.7, 111.4, 110.8, 56.2, 56.1, 51.7, 50.2.

IR (NaCl) cm$^{-1}$ 2993, 2837, 1683(very strong), 1599, 1513, 1269, 1169, 1144, 1025, 915, 774, 731, 714.

HRMS Calculated exact $M^+$ for $C_{16}H_{15}BrO_3$ 334.0205. Found submitted.

Anal. Calculated for $C_{16}H_{15}BrO_3$ C 57.33; H 4.51. Found C 57.11; H 4.48.

**Acid catalyzed hydrolysis of 106a to 111d**

20 mg of **106a** was dissolved in about 0.5 mL of a mixture of 8:1:1 nitromethane: water: trifluoroacetic acid. The resulting mixture was refluxed until all the starting material was converted to the product. The reaction mixture was cooled and neutralized with saturated aqueous sodium bicarbonate. The resulting mixture was extracted twice with 5 mL of ethyl acetate. The combined organic layers were washed with water, dried over sodium sulfate, and concentrated under reduced pressure. The resulting residue was subjected to column chromatography on silica gel. The product **111d** (12 mg, 77.8%)

was eluted with 5% ethyl acetate in hexanes as colorless crystals that undergo slow decomposition. mp 122-123°C.

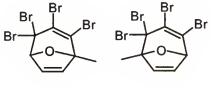
$^1$H-NMR (300 MHz, CDCl3) δ 7.50 (d, J= 8.8 Hz, 2H), 6.98 (d, J= 8.8 Hz, 2H), 6.92 (dd, J= 5.7, 1.66, 1H), 6.60 (dd, J= 5.7, 2.4, 1H), 5.49 (d, J= 1.66, 1H), 5.18 (d, J= 2.4, 1H), 3.86 (s, 3H)

$^{13}$C-NMR (75 MHz, CDCl3) δ 186.4, 161.3, 160.5, 140.3, 131.1, 130.0, 126.6, 114.3, 113.7, 86.9, 85.1, 55.6;

IR (NaCl) cm-1 2974, 2839, 1694(very strong), 1604, 15.8, 1302, 1253, 1179, 1072, 929, 834, 697.

Analysis calculated for $C_{14}H_{11}BrO_3$: C, 54.75, H, 3.61. Found C, 54.55, H, 3.65.

**2,3,4,4-Tetrabromo-1-methyl-8-oxa-bicyclo[3.2.1]octa-2,6-diene and 2,3,4,4-Tetrabromo-1-methyl-8-oxa-bicyclo[3.2.1]octa-2,6-diene (112a/b)**




2-Methyl furan 0.69g (8 mmols) was refluxed in about 2 mL of benzene with 1.5g (4 mmols) of tetrabromocyclopropene. The solvent was removed under reduced pressure and subjected to column chromatography using 5% ethyl acetate in hexanes to elute 1.5g (83%) of a mixture of **112a,b** as a colorless semi-solid. The spectral data of the major isomer is reported.

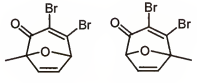
$^1$H NMR (300 MHz, $CDCl_3$) δ 6.76(dd, J=5.7, 1.9 Hz, 1H), 6.32 (d, J=5.7 Hz, 1H), 5.00 (d, J= 1.9 Hz, 1H), 1.94 (s, 3H).

$^{13}$C NMR (75 MHz, $CDCl_3$) δ 142.5, 137.8, 133.6, 130.4, 91.1, 85.1, 70.3, 23.5.

IR (NaCl) $cm^{-1}$2985, 1581, 1387, 1304, 1075, 752, 718.

HRMS Calcd for $C_8H_6Br_4O$ 433.7125. Found 433.7147. Anal. Calcd for $C_8H_6Br_4O$: C, 21.95, H, 1.38. Found C, 22.16, H, 1.39.

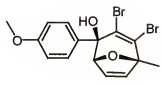
**3,4-Dibromo-5-methyl-8-oxa-bicyclo[3.2.1]octa-3,6-dien-2-one and 3,4-Dibromo-1-methyl-8-oxa-bicyclo[3.2.1]octa-3,6-dien-2-one (113a/b)**




0.2g of (21a/b mixture) upon hydrolysis according to Method A, workup and column chromatography on silica gel using 10% ethyl acetate gave 110 mg (81.5%) of a mixture of **113a,b** as pale yellow oil. The spectra of the major compound are reported. $^1$H NMR (300 MHz, $CDCl_3$) δ 6.75(d, J= 5.7Hz, 1H), 6.49(dd, J= 2.4, 5.7 Hz, 1H), 5.19(d, 2.4 Hz, 1H), 1.82(s, 3H).

$^{13}$C NMR ($CDCl_3$, 75 MHz) δ 184.1, 154.3, 142.7, 131.0, 120.8, 91.7, 87.6, 22.7. IR (NaCl) $cm^{-1}$ 2988, 1708(very strong), 1546, 1186, 1083, 850, 721. Anal. Calcd for $C_8H_6Br_2O_2$: C 32.69; H 2.06. Found: C 32.93; H 2.05.

**3,4-Dibromo-2-(4-methoxy-phenyl)-5-methyl-8-oxa-bicyclo[3.2.1]octa-3,6-dien-2-ol (114)**




Reaction 250 mg of **112a/b** with anisole, as per the general procedure outline for arylation, affords after work and column chromatography with 5% ethyl acetate in hexanes 195 mg (84.8 %) of **114** as colorless crystals. mp 139-141°C. Note (Small amounts of the ortho substitution product is observed in $^1$H NMR).

$^1$H NMR (300 MHz, $CDCl_3$) δ 7.18 (d, J= 8.8 Hz, 2H), 6.88(d, J= 8.8 Hz, 2H), 6.56 (d, J= 5.7 Hz, 1H), 5.76 (dd, J= 5.7, 2.1 Hz, 1H), 4.88 (d, J= 2.1 Hz, 1H), 3.81 (s, 3H), 3.19 (s, 1H), 1.73 (s, 3H).

$^{13}$C-NMR (75 MHz, $CDCl_3$) δ 159.7, 141.7, 136.2, 130.4, 129.6, 129.4, 127.9, 113.8, 89.2, 88.5, 79.3, 55.4, 22.5.

IR (NaCl) cm$^{-1}$ 3442, 2955, 1512, 1250, 1175, 1060, 832, 737, 623.

HRMS Calcd for $C_{15}H_{14}Br_2O_3$ 399.9309. Found 399.9296. An analytical sample was obtained by recrystalizing the compound from 20% ether in pentanes. Anal. Calcd for $C_{15}H_{14}Br_2O_3$: C, 44.81, H 3.51. Found C, 44.61, H 3.51.

**General experimental procedure for Luche reduction of Bicyclic Enones (103a-c).**

The ketones (100 mg) were dissolved in a mixture of 0.2 mL of methylene chloride and 0.8 mL of methanol. The cerium chloride heptahydrate (0.5 eq) was dissolved in 0.2 mL of water and added to the above solution. The solution was stirred at room temperature and 1 equivalent of sodium borohydride was added and stirred for 5 mins. The reaction showed complete conversion of the starting materials to the corresponding

products. The reaction mixture was diluted with 1 mL of water and extracted thrice with 5 mL of ethyl acetate. The ethyl acetate layers were combined, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to afford the crude product as pale yellow oil. The compounds were purified by column chromatography on silica gel using 10-15% ethyl acetate in hexanes.

**3,4-Dibromo-8-oxa-bicyclo[3.2.1]octa-3,6-dien-2-ol (115a)**

The ketone (**103a**) 100 mg was treated as per the general procedure with 55.7 mg of cerium chloride heptahydrate and 13.5 mg of sodium borohydride. The reaction mixture upon workup and purification afforded by column chromatography 96 mg (95%) of **115a** as colorless oil that crystallizes upon standing. mp 102.0-103.0°C.

$^1$H-NMR (300 MHz, $CDCl_3$) δ 6.90 (dd, J= 1.66, 5.94 Hz, 1H), 6.29 (dd, J= 1.91, 5.94 Hz, 1H), 5.24 (dd, J= 1.91, 5.94 Hz, 1H), 4.87 (d, J= 1.91 Hz, 1H), 4.63(dd, J=5.94, 5.74 Hz, 1H), 2.18 (d= 5.47 Hz, 1H).

$^{13}$C-NMR (75 MHz, $CDCl_3$) δ 139.8, 130.5, 129.7, 124.8, 84.5, 81.8, 70.6.

IR (NaCl) $cm^{-1}$ 3389, 1601, 1407, 1296, 1090, 1043, 1002, 978, 943, 873, 720. An analytically pure sample was obtained by recrystalizing the compound from 10% ethyl acetate in hexanes.

Anal. Calcd for $C_7H_6Br_2O_2$: C, 29.82, H, 2.15. Found C, 30.12, H, 2.09.

**3,4-Dibromo-1,5-dimethyl-8-oxa-bicyclo[3.2.1]octa-3,6-dien-2-ol (115b)**

Treatment of 100mg of **103b** afforded 97mg (96%) of **115b** as (mixture of exo/endo alcohols) as colorless oil. The spectral data for the major compound is reported.

$^1$H-NMR (300 MHz, CDCl3) δ 6.54 (d, J= 5.71 Hz, 1H), 6.00 (d, J= 5.71 Hz, 1H), 4.24 (s, 1H), 2.44 (s, 1H), 1.61 (s, 3H), 1.60 (s, 3H).

$^{13}$C-NMR (75 MHz, CDCl3) δ 142.5, 133.8, 134.6, 126.8, 88.8, 88.2, 76.5, 22.6, 22.1.

IR (NaCl) cm$^{-1}$ 3424 (br), 2978, 1590, 1449, 1373, 1296, 1173, 1072, 1049, 937, 879 737.

Anal. Calcd for $C_9H_{10}Br_2O_2$: C 34.87, H 3.25. Found C 34.44, H 3.12.

**3,4-Dibromo-bicyclo[3.2.1]octa-3,6-dien-2-ol (24c)**

Treatment of 100mg of **103c** afforded 98mg (97%) of **115c** as colorless oil.

$^1$H-NMR (300 MHz, CDCl3) δ 6.69 (dd, J= 5.7, 2.85 Hz, 1H), 6.08 (dd, J= 5.7, 2.85 Hz, 1H), 4.48 (d, J= 5.47 Hz, 1H), 3.34-3.17 (m, 2H) 2.16-2.10 (m, 3H).

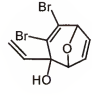
$^{13}$C-NMR (75 MHz, CDCl3) δ 142.2, 133.0, 132.8, 124.8, 74.1, 51.9, 46.5, 44.1; IR (NaCl)cm$^{-1}$ 3370, 2942, 2868, 1600, 1109, 1030, 744.

Anal. Calcd for $C_8H_8Br_2O$: C 34.32, H 2.88. Found C 34.56, H 2.85.

**General experimental procedure for addition of Grignard reagents to 3,4-Dibromo-8-oxa-bicyclo[3.2.1]octa-3,6-dien-2-one (103a).**

The dibromoeneone (8a) 100mg (0.35 mmols) was dissolved in about 2 mL of dry THF. The resulting solution was cooled to 0°C. The desired Grignard (1.2 eq, 0.42 mmols) was added dropwise over a period of 5 mins. The solution was stirred at 0°C for about 5-10 mins and the TLC was checked for completion of the reaction. The reaction mixture was quenched with aqueous sodium bicarbonate and extracted thrice with 10 mL of ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated to dryness. The resulting brown semisolid was purified by column chromatography to afford the 1,2 addition products as crystalline solids.

**3,4-Dibromo-2-vinyl-8-oxa-bicyclo[3.2.1]octa-3,6-dien-2-ol (115d)**




Reaction of 100 mg of **103a** with 1.2 eq of vinylmagnesiumbromide as described in the general procedure followed by workup and column chromatography afforded 80 mg (73.4%) of the product as colorless crystals. mp 67.0-70.0°C.

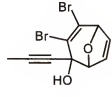
$^1$H-NMR (300 MHz, $CDCl_3$) δ 6.85(dd, J=5.95, 1.67, 1H), 6.26(dd, J=5.95, 2.14, 1H), 6.10(m, 1H), 5.36(m, 2H), 4.90(d, J= 2.14, 1H), 4.84(d, J= 1.67, 1H), 2.18(br s, 1H).

$^{13}$C-NMR (75 MHz, $CDCl_3$) δ 140.4, 139.9, 131.1, 129.3, 126.8, 116.2, 85.9, 84.4, 76.5.

IR (NaCl) $cm^{-1}$ 3437 (br, s), 1602, 1035, 921, 723.

An analytically pure sample was obtained by recrystalizing the compound from 10% ethyl acetate in hexanes. Anal. Calcd for $C_9H_8Br_2O_2$: C, 35.10, H, 2.62. Found C, 35.31, H, 2.51.

**3,4-Dibromo-2-prop-1-ynyl-8-oxa-bicyclo[3.2.1]octa-3,6-dien-2-ol (115e)**




Reaction of 100 mg of **103a** with 1.2 eq of propynylmagnesiumbromide as described in the general procedure followed by workup and column chromatography afforded 105 mg (92%) of **115e** the product as colorless crystals. mp 149.0-150°C.

$^1$H-NMR (300 MHz, $CDCl_3$) δ 6.82, (dd, J=5.94, 1.66, 1H), 6.22, (dd, J=5.94, 2.14, 1H), 5.19, (d, J=2.14), 4.85, (d, J=1.66), 2.50(br s, 1H), 1.85(s, 3H).

$^{13}$C-NMR (75 MHz, $CDCl_3$) δ 139.5, 130.5, 129.2, 125.7, 86.4, 84.4, 82.6, 79.6, 70.2, 4.0.

IR (NaCl) $cm^{-1}$ 3412, 2966, 2225, 1601, 1278, 1055, 1031, 926, 732. An analytically pure sample was obtained by recrystalizing the compound from 10% ethyl acetate in hexanes.

Anal. Calcd for $C_{10}H_8Br_2O_2$: C, 37.54, H, 2.52. Found C, 37.73, H, 2.79.

**3,4-Dibromo-2-phenyl-8-oxa-bicyclo[3.2.1]octa-3,6-dien-2-ol (115f)**

Reaction of 100 mg of **103a** with 1.2 eq of phenylmagnesiumbromide as described in the general procedure followed by workup and column chromatography afforded 103 mg (81 %) of the product (**115f**) as colorless crystals. mp 99.0-100.5°C.

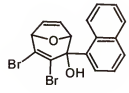
$^1$H-NMR (300 MHz, $CDCl_3$) δ 7.61-7.30 (m, 5H), 6.87 (dd, J= 5.94, 1.66 Hz, 1H), 6.42 (dd, J= 5.94, 1.90 Hz, 1H), 5.00 (d, J= 1.66 Hz, 1H), 4.95 (d, J= 1.90 Hz, 1H), 2.51 (s, 1H).

$^{13}$C-NMR (75 MHz, $CDCl_3$) δ 143.5, 139.6, 131.8, 129.9, 128.7, 128.5, 127.0, 126.1, 87.6, 84.4, 78.5.

IR (NaCl) $cm^{-1}$ 3432, 3059, 1604, 1493, 1448, 1304, 1058, 1032, 920, 736, 721, 699. An analytically pure sample was obtained by recrystalizing the compound from 20% diethyl ether in pentanes.

Anal. Calcd for $C_{10}H_8Br_2O_2$: C, 37.54, H, 2.52. Found C 43.61, H 2.82. Found C 43.82, H 2.72.

**3,4-Dibromo-2-naphthalen-1-yl-8-oxa-bicyclo[3.2.1]octa-3,6-dien-2-ol (115g)**



Reaction of 100 mg of **103a** with 1.2 eq of naphthylmagnesiumbromide as described in the general procedure followed by workup and column chromatography afforded 130.0 mg (89%) of **115g** as colorless crystals. mp 202.0-204.0°C.

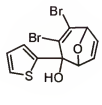
$^1$H-NMR (300 MHz, $CDCl_3$) δ 8.81(d. J=3.1 Hz, 1H), 7.82-7.92 (m, 2H), 7.41-7.59 (m, 4H), 6.96 (dd, J= 5.94, 1.67, 1H), 6.58 (dd, J= 5.94, 1.91, 1H), 5.66 (d, J= 1.91 Hz, 1H), 4.96 (d, J= 1.67 Hz, 1H), 2.80-2.90 (br s, 1H).

$^{13}$C-NMR (75 MHz, $CDCl_3$) δ 139.3, 136.7, 135.3, 131.3, 130.8, 130.4, 130.2, 129.8, 128.5, 127.4, 126.4, 125.9, 125.7, 124.9, 85.9, 84.4, 81.7.

IR (NaCl) $cm^{-1}$ 3428, 3049, 1597, 1508, 1287, 1057, 777.

HRMS calculated for $C_{17}H_{12}Br_2O_2$ 405.9204. Found 405.9293. An analytically pure sample was obtained by recrystalizing the compound from 10% ethyl acetate in hexanes. Anal. Calcd for $C_{17}H_{12}Br_2O_2$: C, 50.03, H, 2.96. Found C, 50.27 H, 2.94.

**3,4-Dibromo-2-thiophen-2-yl-8-oxa-bicyclo[3.2.1]octa-3,6-dien-2-ol (115h)**



100 mg of **103a** was treated with 1.2 eq of thiophenyl-2-magnesium bromide as described above. The resulting solution upon work up and column chromatography afforded 115 mg (88%) of **115h** as pale yellow crystals. mp 52.0-55.0°C.

$^1$H-NMR (300 MHz, CDCl3) δ 7.30 (dd, J= 4.99, 1.19 Hz, 1H), 7.15 (dd, J= 3.68, 1.99 Hz, 1H), 7.00 (dd, J= 4.99, 3.68, 1H), 6.95 (dd, J= 5.94, 1.66 Hz, 1H), 6.39 (dd, J= 5.94, 2.14 Hz, 1H), 5.13 (d, J= 2.14 Hz, 1H), 4.99 (d, J= 1.99 Hz, 1H).

$^{13}$C NMR (75 MHz, $CDCl_3$) δ 148.0, 140.0, 131.3, 130.4, 127.2, 126.8, 125.9, 125.5, 87.4, 84.4, 76.8.

IR (NaCl) cm$^{-1}$ 3412, 1603, 1304, 1233, 1104, 1037, 925, 737, 712.

HRMS calculated for $C_{11}H_8O_2BrS$ 361.8611. Found 361.8612. Anal. Calcd $C_{11}H_8O_2BrS$: C 36.29, H 2.21. Found C 36.38, H 2.14.

**General experimental procedure for addition of cuprates to 3,4-Dibromo-8-oxa-bicyclo[3.2.1]octa-3,6-dien-2-one (103a)**

Purified CuI[80] (81.6mg, 0.43 mmols) was suspended in dry diethyl ether and cooled to -78°C. The desired alkyl or aryl lithium (0.79 mmols) was added dropwise over a period of 5 min. The resulting solution was warmed and kept at -10°C for 30min. The resulting cuprate was then cooled to -78°C. The dibromoenone (100mg, 0.35 mmols) was dissolved in about 2 mL of ether and the resulting solution was added to the cuprate dropwise over a period of 5 mins. The resulting solution was stirred at -78°C and periodically monitored by tlc. Upon completion of reaction the solution was warmed to 0°C and treated with 5 mL of saturated aqueous ammonium chloride. The solution was extracted thrice with 10 mL of diethyl ether. The organic layer was dried over anhydrous sodium sulfate and concentrated to dryness. The resulting brown semisolid was purified

by column chromatography over silica gel using 5%-10% ethyl acetate and hexanes as solvent.

**3-Bromo-4-methyl-8-oxa-bicyclo[3.2.1]octa-3,6-dien-2-one (116a)**

100 mg of **103a** was treated with 1.1 equivalents of $Me_2CuLi$ as per the general procedure. The reaction was followed by workup and column chromatographic purification to afford 65mg (84.4%) of the product as a brown semisolid.

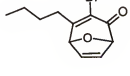
$^1$H-NMR (300 MHz, $CDCl_3$) δ 6.92 (dd, J= 2.14, 5.71 Hz, 1H), 6.56 (dd, J= 2.13, 5.23 Hz, 1H), 5.16(d, J= 2.14 Hz, 1H), 5.12(d, J= 2.13 Hz, 1H), 2.12(s, 3H).

$^{13}$C-NMR (75 MHz, $CDCl_3$) δ 185.8, 162.0, 139.4, 131.5, 115.5, 86.8, 84.3, 20.4.

IR (NaCl) cm$^{-1}$ 2980, 1707(very strong), 1603, 1240, 1068, 929, 764, 692, 625.

HRMS Calculated exact $M^+$ for $C_8H_7BrO_2$: 213.9629. Found 213.9619.

**3-Bromo-4-butyl-8-oxa-bicyclo[3.2.1]octa-3,6-dien-2-one (116b)**




100 mg of **103a** was treated with 1.1 equivalents of $Bu_2CuLi$ as per the general procedure. The reaction was followed by workup and column chromatographic purification to afford 80 mg (88%) of the product as brown oil.

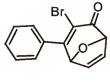
$^1$H-NMR (300 MHz, $CDCl_3$) δ 6.85 (dd, J=1.90, 5.71 Hz, 1H), 6.54 (dd, J=2.37, 5.71 Hz, 1H), 5.18 (d, J= 1.90 Hz, 1H), 5.10(d, J=2.37 Hz, 1H), 2.56-2.36 (m, 2H), 1.62-1.36 (m, 4H), 0.97 (t= 7.13 Hz, 3H).

$^{13}$C-NMR (75 MHz, $CDCl_3$) δ 186.2, 165.3, 140.1, 131.2, 115.2, 83.9, 83.3, 34.3, 28.6, 22.8, 14.0.

IR (NaCl) cm$^{-1}$ 2959, 1705, 1594, 1063.

HRMS Calculated exact $M^+$ for $C_{11}H_{13}BrO_2$ 256.0099. Found 256.0103. Anal. Calcd C 51.38; H 5.10. Found C 51.49, H 5.20.

**3-Bromo-4-phenyl-8-oxa-bicyclo[3.2.1]octa-3,6-dien-2-one(116c)**




100 mg of **103a** was treated with 1.1 equivalents of $Ph_2CuLi$ as per the general procedure. The reaction was followed by workup and column chromatographic purification to afford 77mg (78%) of the product as a brown semisolid.

$^1$H-NMR (300 MHz, $CDCl_3$) δ 7.45(s, 5H), 6.96(dd, J=1.90, 5.71 Hz, 1H), 6.62 (dd, J=2.40, 5.71 Hz, 1H), 5.46(d, J=1.90 Hz, 1H), 5.20(d, J=2.40 Hz, 1H).

$^{13}$C-NMR (75 MHz, $CDCl_3$) δ 186.3, 161.1, 140.4, 134.7, 131.1, 130.3, 128.9, 127.9, 114.8, 86.9, 85.2.

IR (NaCl) cm$^{-1}$2979, 1699, 1585, 1186, 1072, 697.

HRMS Calculated exact $M^+$ for $C_8H_7BrO_2$ 275.9786. Found 275.9762. Analytical sample was obtained by recrystalizing the compound from 20% ether in pentanes. Anal. Calcd C 56.34; H 3.27. Found C 56.10; H 3.19.

**3-Bromo-4,4-dimethyl-8-oxa-bicyclo[3.2.1]oct-6-en-2-one(117)**

50 mg of **103a** was treated with 2.2 eq of $Me_2CuLi$ as per the general procedure monitored by tlc and worked up. The pale brown semisolids were subjected to column chromatography to afford 30 mg of **117** as pale brown oil.

$^1$H-NMR (300 MHz, $CDCl_3$) δ 6.60-6.48 (m, 2H), 4.94 (s, 1H), 4.76 (d, J= 1.9 Hz, 1H), 4.72 (d, J= 1.9 Hz, 1H), 1.35 (s, 3H), 1.08 (s, 3H).

$^{13}$C-NMR (75 MHz, $CDCl_3$) δ 194.2, 134.2, 132.7, 88.4, 85.6, 62.9, 25.4, 23.3.

IR (NaCl) $cm^{-1}$2982, 1710 (very strong), 1587, 1188, 1070, 702.

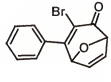
HRMS Calculated exact $M^+$ for $C_9H_{10}BrO_2$: 229.9942. Found 299.9960.

**General procedure for Suzuki couplings**

In a dry screw cap tube 1mL of dry acetonitrile was taken and degassed by bubbling argon through it. Then the following reagents were added in order 8.1 mg (0.036 mmols, 10 mol%) of Palladium acetate, 18 µL of triethyl amine (0.017 mmols, 50 mol%) and 37.5 mg of triphenylphosphine (0.014 mmols, 40 mol%) and stirred for 15 minutes. The dissolution of palladium acetate if followed by the formation of a bright yellow colored precipitate. To the resulting solution 100 mg of **103a** (0.035 mmols), 54.3

mg of 4-Methoxyphenyl boronic acid (0.035 mmols), and 108.4 mg of silver carbonate (0.035 mmols) were added and the stirring was continued at room temperature till all the starting dibromoenone was consumed (usually the reaction mixture was stirred overnight). The crude reaction mixture was subjected to Soxhlet extraction using 25 mL of ethyl acetate. The crude extract was subjected to column chromatography using 5% ethyl acetate in hexanes to 10 % ethyl acetate in hexane to afford the desired products. In order to get good yields it is important to perform the Soxhlet extraction. If the crude reaction mixture is directly subjected to column chromatography, (after removing the acetonitrile) the yields of the products are significantly lower (in the order of 40-50%). All the products are colorless to pale yellow crystalline materials that slowly turn brown on exposure to light at room temperature.

**3-Bromo-4-phenyl-8-oxa-bicyclo[3.2.1]octa-3,6-dien-2-one(116c)**




50 mg of **103a** was subjected to Suzuki coupling (the quantities of all the reagents were halved with respect to the numbers reported in the general procedure) to afford 39.8 mg of **116c** as crystalline material.

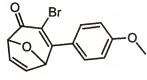
$^{1}$H-NMR (300 MHz, $CDCl_3$) δ 7.45(s, 5H), 6.96(dd, J=1.90, 5.71 Hz, 1H), 6.62 (dd, J=2.40, 5.71 Hz, 1H), 5.46(d, J=1.90 Hz, 1H), 5.20(d, J=2.40 Hz, 1H).

$^{13}$C-NMR (75 MHz, $CDCl_3$) δ 186.3, 161.1, 140.4, 134.7, 131.1, 130.3, 128.9, 127.9, 114.8, 86.9, 85.2.

IR (NaCl) $cm^{-1}$2979, 1699, 1585, 1186, 1072, 697.

HRMS Calculated exact $M^+$ for $C_8H_7BrO_2$ 275.9786. Found 275.9762. Analytical sample was obtained by recrystalizing the compound from 20% ether in pentanes. Anal. Calcd C 56.34; H 3.27. Found C 56.10; H 3.19.

**3-Bromo-4-(4-methoxy-phenyl)-8-oxa-bicyclo[3.2.1]octa-3,6-dien-2-one (111d)**




100 mg of 50 mg of **103a** was subjected to Suzuki coupling with 4-methoxy phenyl boronic acid to afford 80.4 mg (73.3 %) of **111d** as colorless crystals. mp 122-123°C.

$^1$H-NMR (300 MHz, CDCl3) δ 7.50 (d, J= 8.8 Hz, 2H), 6.98 (d, J= 8.8 Hz, 2H), 6.92 (dd, J= 5.7, 1.66, 1H), 6.60 (dd, J= 5.7, 2.4, 1H), 5.49 (d, J= 1.66, 1H), 5.18 (d, J= 2.4, 1H), 3.86 (s, 3H).

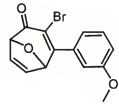
$^{13}$C-NMR (75 MHz, CDCl3) δ 186.4, 161.3, 160.5, 140.3, 131.1, 130.0, 126.6, 114.3, 113.7, 86.9, 85.1, 55.6.

IR (NaCl) $cm^{-1}$ 2974, 2839, 1694(very strong), 1604, 15.8, 1302, 1253, 1179, 1072, 929, 834, 697.

HRMS Calculated exact $M^+$ for $C_{14}H_{11}BrO_3$ 305.9891. Found 305.9854.

Analysis calculated for $C_{14}H_{11}BrO_3$: C, 54.75, H, 3.61. Found C, 54.55, H, 3.65.

**3-Bromo-4-(3-methoxy-phenyl)-8-oxa-bicyclo[3.2.1]octa-3,6-dien-2-one (119a)**



100 mg of **103a** affords 86.7 mg of **119a** as pale brown amorphous solids.

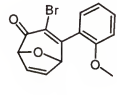
$^1$H-NMR (300 MHz, CDCl3) δ 7.44-7.36 (m, 1H), 7.02-6.94 (m, 4H), 6.62 (dd, J= 5.7, 2.37 Hz, 1H), 5.45 (d, J= 1.9 Hz, 1H), 5.20 (d, J= 2.37 Hz, 1H), 3.80 (s, 3H).

$^{13}$C-NMR (75 MHz, CDCl3) δ 186.3, 161.0, 159.7, 140.4, 135.9, 131.0, 130.1, 119.9, 115.8, 114.8, 113.5, 86.9, 85.2, 55.6.

IR (NaCl) cm$^{-1}$ 2966, 1698 (very strong), 1577, 1485, 1428, 1291, 1214, 1165, 1024, 931, 707.

Analysis calculated for $C_{14}H_{11}BrO_3$: C, 54.75, H, 3.61. Found C, 53.99, H, 3.74.

**3-Bromo-4-(2-methoxy-phenyl)-8-oxa-bicyclo[3.2.1]octa-3,6-dien-2-one (119b)**



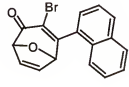
100 mg of **103a** affords 86.7 mg of **119a** as pale brown amorphous solids.

$^1$H-NMR (300 MHz, CDCl3) δ 7.46-7.40 (m, 1H), 7.30 (dd, J= 7.60, 1.90 Hz, 1H), 7.07-6.95 (m, 3H), 6.56 (dd, J= 5.70, 2.4 Hz, 1H), 5.41 (d, J= 1.66, 1H), 5.19 (d, J= 2.38, 1H), 3.90 (s, 3H).

$^{13}$C-NMR (75 MHz, CDCl3) δ 186.5, 161.6, 156.3, 144.0, 141.5, 131.7, 130.11, 130.08, 120.9, 116.0, 111.4, 87.0, 84.5, 55.8.

IR (NaCl) cm$^{-1}$ 2968, 1699, 1486, 1256, 1016, 926, 756. Analysis calculated for $C_{14}H_{11}BrO_3$: C, 54.75, H, 3.61. Found C, 54.49, H, 3.53.

**3-Bromo-4-naphthalen-1-yl-8-oxa-bicyclo[3.2.1]oct-6-en-2-one (119c)**




100 mg of **103a** affords 92.0 mg (78%) of **119c** as colorless crystals.

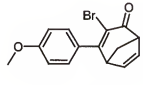
$^{1}$H-NMR (300 MHz, CDCl3) δ 8.00-7.86 (m, 5H), 7.62-7.5 (m, 4H), 7.00 (dd, J= 5.7, 1.9 Hz, 1H), 6.65, (dd, J= 5.7, 2.38 Hz, 1H), 5.58 (d, J= 1:90 Hz, 1H), 5.24 (d, J= 2.38 Hz, 1H).

$^{13}$C-NMR (75 MHz, CDCl3) δ 186.3, 140.5, 133.6, 133.0, 132.0, 131.2, 130.9, 128.8, 128.7, 128.13, 128.08, 127.9, 127.2, 124.8, 87.0, 85.3.

IR (NaCl) cm$^{-1}$ 3057, 2979, 1699, 1575, 1195, 1072, 931, 749, 734.

Analysis calculated for $C_{17}H_{13}BrO_3$: C, 62.41, H, 3.39. Found C, 62.41, H, 3.25.

**3-Bromo-4- (4-methoxy-phenyl)-bicyclo[3.2.1]octa-3,6-dien-2-one (111b)**




100 mg of **102d** was reacted with 54.7 mg of 4-Methoxy phenyl boronic acid to yield 77.3 mg (70.6%) of **111b** as a colorless crystalline solids. mp 131-132°C

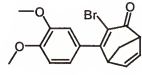
$^1$H-NMR (300 MHz, $CDCl_3$) δ 7.45 (d, J = 8.7 Hz, 2H), 6.96 (d, J = 8.7 Hz, 2H), 6.80 (m, 1H), 6.32, (m 1H), 3.86 (s, 3H), 3.66 (m, 2H), 2.72 (d, J= 10.35 Hz, 1H), 2.48-2.58 (m, 1H).

$^{13}$C-NMR (75 MHz, $CDCl_3$) δ 191.2, 163.9, 160.5, 142.9, 133.2, 131.0, 129.5, 115.6, 113.8, 56.2, 55.5, 51.7, 50.2. IR (NaCl) cm$^{-1}$ 2966, 2838, 1683(very strong), 1604, 1507, 1250, 1178, 1027, 832, 773, 713.

HRMS Calculated exact $M^+$ for $C_{15}H_{13}BrO_2$ 304.0099. Found 304.0094.

Anal. Calculated for $C_{15}H_{13}BrO_2$: C, 59.04; H, 4.29. Found C 58.90; H 4.29.

**3-Bromo-4-(3,4-dimethoxy-phenyl)-bicyclo[3.2.1]octa-3,6-dien-2-one (111c)**




100 mg of **102d** was reacted with 65.5 mg of 3,4-dimethoxy phenyl boronic acid and followed by work up and column chromatography to afford 100.5 mg (83%) of **111c** as a colorless crystalline solid. mp 117-119°C.

$^1$H-NMR (300 MHz, $CDCl_3$) δ 7.06 (s, 1H), 7.04 (d, J = 8.8 Hz, 1H), 6.92 (d, J = 8.8 Hz, 1H), 6.82 (m, 1H), 6.34 (m, 1H), 3.94 (s, 3H), 3.92 (s, 3H) 3.70-3.64 (m, 2H), 2.74 (d, J = 10.35 Hz, 1H), 2.60-2.50 (m, 1H).

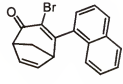
$^{13}$C-NMR (75 MHz, $CDCl_3$) δ 191.1, 163.9, 150.0, 148.5, 142.8, 133.2, 131.2, 120.9, 115.7, 111.4, 110.8, 56.2, 56.1, 51.7, 50.2.

IR (NaCl) cm$^{-1}$ 2993, 2837, 1683(very strong), 1599, 1513, 1269, 1169, 1144, 1025, 915, 774, 731, 714.

HRMS Calculated exact $M^+$ for $C_{16}H_{15}BrO_3$ 334.0205. Found submitted.

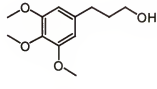
Anal. Calculated for $C_{16}H_{15}BrO_3$ C 57.33; H 4.51. Found C 57.11; H 4.48.

**3-Bromo-4-naphthalen-1-yl-bicyclo[3.2.1]octa-3,6-dien-2-one (119d)**




100 mg of **102d** was reacted with 62.0 mg of 1-Naphthyl boronic acid and followed by work up and column chromatography to afford 60.0 mg of **119d** as a colorless crystalline solid.

**3-(3,4,5-Trimethoxy-phenyl)-propan-1-ol**



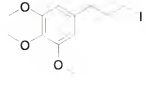

Method A: 3-(3,4,5-Trimethoxy-phenyl)-1-propionic acid 6.0g (0.025 mols) was dissolved in 25 mL of dry THF. A suspension of 1.2g (0.03 mols) of Lithium aluminum hydride was made in 25 mL of dry THF and cooled in an ice bath. The solution containing trimethoxy phenyl propionic acid was added dropwise over a period of 20 mins. The resulting solution was slowly brought to room temperature and refluxed for 5 hrs. The resulting mixture was worked up according to the Fieser procedure. The yield of the crude was alcohol was 5.5g (96.5 %) and it was used in subsequent steps with out further purification.

Method B: 3-(3,4,5-Trimethoxy-phenyl)-1-propionic acid 2.0g (0.0083 mols) was dissolved in 15 mL of dry THF and cooled in an ice bath. 8.3 mL of 1M Borane:THF was added dropwise and stirred for 1 hr. The solution was allowed to gradually warm up to room temperature. The THF was removed under reduced pressure and the remaining organic residue was partitioned between 20mL of ethyl acetate and 20 mL of 5% potassium carbonate. The ethyl acetate layer was washed with 15-20mL of water, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to afford 1.9 g (> 95%) of the alcohol as colorless viscous oil. The crude was used without further purification.

$^{1}$H-NMR (300 MHz, $CDCl_3$) δ 6.40 (s, 2H), 3.84 (s, 6H), 3.80(s, 3H), 3.68 (t, J= 7.8 Hz, 2H), 2.40-2.50 (br s, 1H), 1.89 (m, 2H), 1.21 (t, J = 7.5 Hz, 2H).

$^{13}$C-NMR (75 MHz, $CDCl_3$) δ 153.2, 137.9, 136.0, 105.2, 61.9, 60.8, 56.0, 34.3, 32.6.

**5-(3-Iodo-propyl)-1,2,3-trimethoxy-benzene**




1.5g (0.007 mols) of 3-(3,4,5-trimethoxy-phenyl)-propan-1-ol was dissolved in 50 mL of benzene to this solution was added 2.6g (0.01 mols) of triphenylphosphine and 0.68g (0.01 mols) of imidazole and stirred at room temperature. Iodine 2.2g(0.0086 mols) was dissolved in 25 mL of benzene and added dropwise to the mixture of alcohol, triphenylphosphine and imidazole in 15 minutes. The solution was stirred for another 30

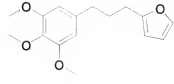
minutes. The benzene layer was washed with 25 mL of 5% aqueous sodium thiosulfate, followed by washing with 25mL of water. The organic layer was dried over anhydrous sodium sulfate, and the benzene was removed under reduced pressure. The organic residue was subjected to column chromatography and the product (1.8g, 78%) was obtained as colorless oil.

$^1$H-NMR (300 MHz, $CDCl_3$) δ 6.40 (s, 2H), 3.84 (s, 6H), 3.80 (s, 3H), 3.2 (t, J= 6.65 Hz, 2H), 2.68 (t, J= 6.65 Hz, 2H), 2.10 (m, 2H)

$^{13}$C-NMR (75 MHz, $CDCl_3$) δ 153.4, 136.5, 136.3, 105.6, 61.0, 56.3, 36.7, 35.0, 6.7.

HRMS Calculated for $C_{12}H_{17}IO_3$ 336.0222. Found 336.0226.

**2-[3-(3,4,5-Trimethoxy-phenyl)-propyl]-furan (148)**



Furan 0.404g (0.006 mols) was dissolved in about 5 mL of THF and cooled to -78°C in an acetone-dry ice bath. To this cooled solution was added 1.9 mL of nBuLi (2.35M, 0.0045 mols) and the resulting solution was stirred and warmed to room temperature and kept at room temperature for about 20 minutes. The resulting 2-Furyl Lithium was cooled down to -78°C. 5-(3-Iodo-propyl)-1,2,3-trimethoxy-benzene, 1.0g (0.003 mols) was dissolved in about 5 mL of dry THF and added dropwise to the cold 2-furyl lithium solution with stirring and gradually allowed to warm up to room temperature. The resulting reaction mixture was checked by tlc for complete

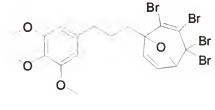
consumption of starting material. The resulting organic material was partitioned between 25 mL of ethyl acetate and 15mL water to remove the inorganic salts. The organic layer was dried over saturated sodium sulfate and concentrated under reduced pressure. The remaining organic residue was subjected to column chromatography and the product was eluted with 15% ethyl acetate in hexanes to afford 0.746 g (90.8 %) of the product as a colorless viscous oil.

$^{1}$H-NMR (300 MHz, $CDCl_3$) δ 7.35 (dd, J = 1.76, 0.87 Hz, 1H), 6.40 (s, 2H), 6.30 (dd, J = 2.93, 1.76 Hz, 1H), 6.01 (dd, J = 2.93, 0.87 Hz, 1H), 3.84 (s, 6H), 3.80 (s, 3H), 2.67 (t, J= 7.3 Hz, 2H), 2.60 (t, J= 7.3 Hz, 2H), 1.96 (m, 2H).

$^{13}$C-NMR (75 MHz, $CDCl_3$) δ 156.0, 153.2, 141.00, 137.9, 110.3, 105.4, 105.1, 61.0, 56.2, 35.8, 29.9, 27.6.

HRMS Calculated for $C_{16}H_{20}O_4$ 276.1362. Found 276.1363. Analysis calcd for $C_{16}H_{20}O_4$: C 69.54; H 7.30. Found C 69.47; H 7.34.

**2,3,4,4-Tetrabromo-5-[3-(3,4,5-trimethoxy-phenyl)-propyl]-8-oxa-bicyclo[3.2.1]octa-2,6-diene and 2,3,4,4-Tetrabromo-1-[3-(3,4,5-trimethoxy-phenyl)-propyl]-8-oxa-bicyclo[3.2.1]octa-2,6-diene (149a,b)**




0.5g (0.0018 mols) of 2-[3-(3,4,5-Trimethoxy-phenyl)-propyl]-furan was dissolved in 2mL of benzene and to this solution was added 0.774g (0.0022 mols) of tetrabromocyclopropene. The resulting solution (starts to turn dark brown almost

immediately at room temperature) was gently refluxed till all the starting furan was consumed by tlc. The benzene was removed under reduced pressure and the black organic residue was subjected to column chromatography and the product was eluted with 20% ethyl acetate in hexanes as a pale brown semi-solid. Yield 1.0g (88%).

$^1$H-NMR (300 MHz, $CDCl_3$) δ 6.78 (dd, J= 5.95, 1.9 Hz, 1H), 6.62 (d, J= 5.7 Hz, 1H), 6.42 (s, 2H), 6.40(s, 2H), 6.38 (dd, J= 5.95, 1.6 Hz, 1H), 6.28 (d, J= 5.7 Hz, 1H), 5.62 (d, 1.9 Hz, 1H), 5.00 (d, 1.6 Hz, 1H), 3.86 (s, 12H), 3.82 (s, 6H), 2.70-2.35 (m, 6H), 2.1-1.5 (m, 6H).

$^{13}$C-NMR (75 MHz, $CDCl_3$) δ 153.3, 141.7, 137.97, 137.914, 137.71, 136.3, 135.2, 131.9, 130.4, 129.5, 127.8, 127.1, 105.46, 105.47, 95.4, 90.96, 90.92, 84.9, 70.8, 62.1, 61.0, 56.3, 36.52, 36.37, 35.1, 34.0, 26.3, 25.5.

HRMS calcualated $M^+$ for $C_{19}H_{20}Br_4O_4$ 627.8095. Found 627.8096.

APPENDIX A
KINETICS OF REARRANGEMENT: EXPERIMENTAL DATA

**Kinetic studies**

The reaction was monitored by H1 NMR at 500 MHz on a Varian Inova spectrometer equipped with a 5 mm indirect detection probe. Ca. 5 mg of pure sample was dissolved in 0.75 ml of solvent and the tubes were sealed to prevent evaporation. The reactions in toluene-*d8* were run at 40, 60 and 80 °C; the reaction in DMF-*d7* at 20, 40, 60 and 80 °C. During the reaction, the temperature was regulated within 0.1 °C, by the variable temperature unit of the spectrometer. At the end of the reaction, a standard sample of ethylene glycol was allowed to reach the temperature for 1 hour and then the temperature was monitored every minute for 20 minutes, allowing a measurement of an average temperature within 0.02°C. During the reaction typically 100 spectra were collected, at time intervals of 30 minutes at 20 and 40°C, 12 minutes at 60°C and 6 minutes at 80°C. Each spectrum was collected with the maximum number of 6 s scans. The integrals of the signals of the starting material (SM) were normalized against the integrals of the residual signals of the solvent. The plots $\ln([SM_{initial}]/[SM])$ *vs.* time afforded the rates ($k$), with a typical $R^2$ of 0.9996. The plots $\ln(k)$ *vs.* 1/T fitted a line with a typical $R^2$ of 0.9999. The enthalpy and entropy of activation were calculated from the slope ($a$) and intercept ($b$) of this line as $\Delta H = -a*8.31/4184$ (kcal/mole) and $\Delta S = (b-23.76)*8.31/4.184$ (cal/mole/K). The kinetic plots are provided below and X-ray crystal data for **90** are provided in Appendix C.

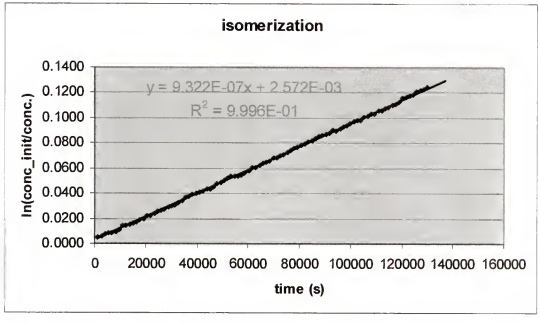



Figure 1: Isomerization of **89** at 40°C in Toluene-$d_8$

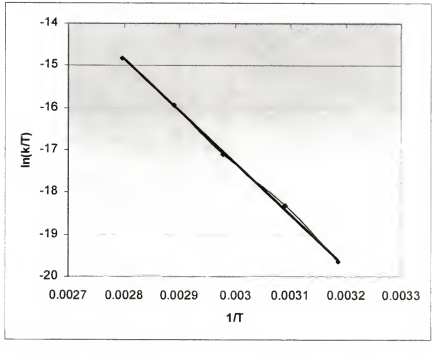



Figure 2: Plot of ln(k/T) Vs 1/T for **89** in Toluene-$d_8$

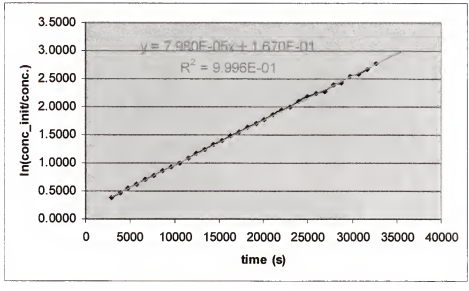



Figure 3: Isomerization of **89** at 40°C in DMF-$d_7$

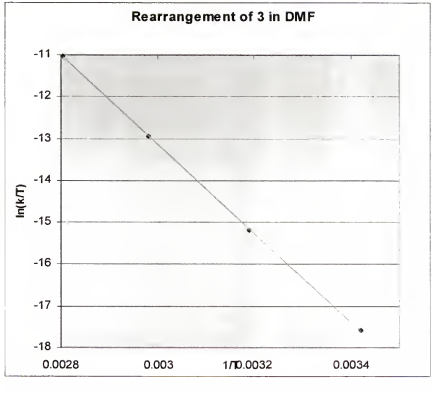



Figure 4: Plot of ln(k/T) Vs 1/T for **89** in DMF-$d_7$

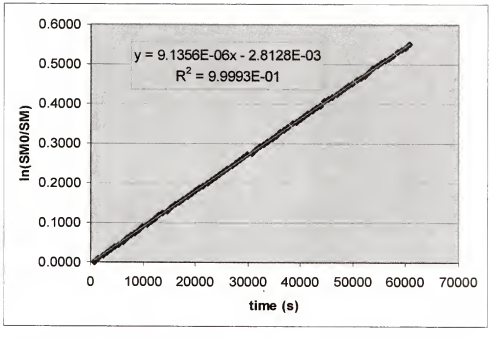



Figure 5: Isomerization of **90** at 60°C in Toluene-$d_8$

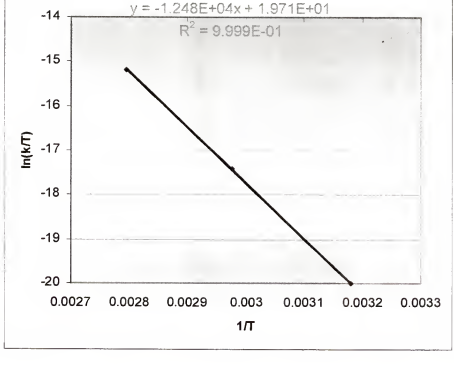
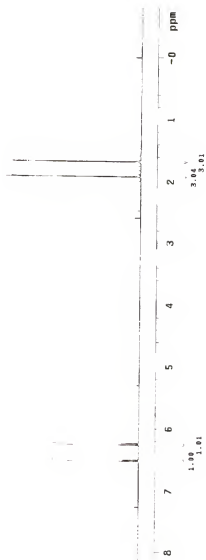
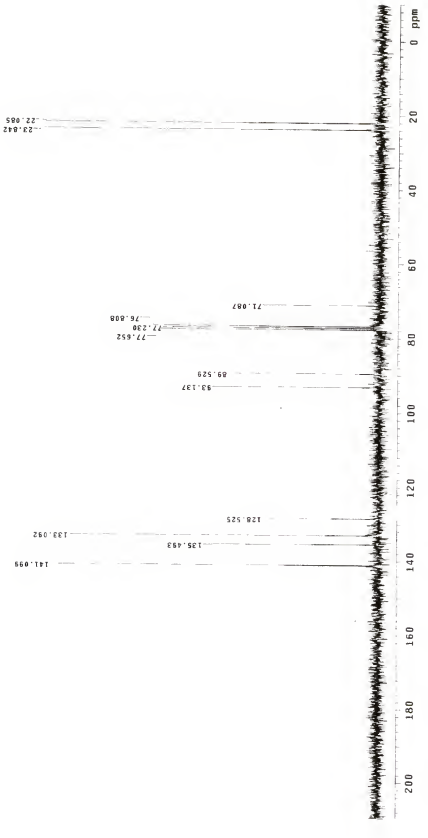


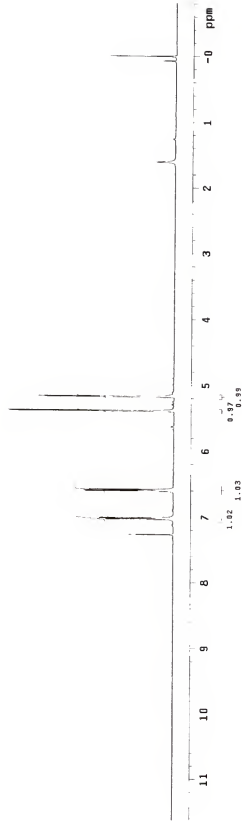

Figure 4: Plot of ln(k/T) Vs 1/T for **90** in Toluene-$d_8$

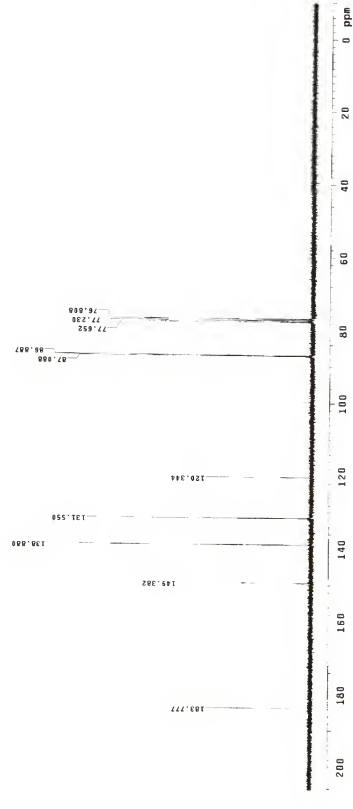
APPENDIX B
SPECTRA OF SELECTED COMPOUNDS



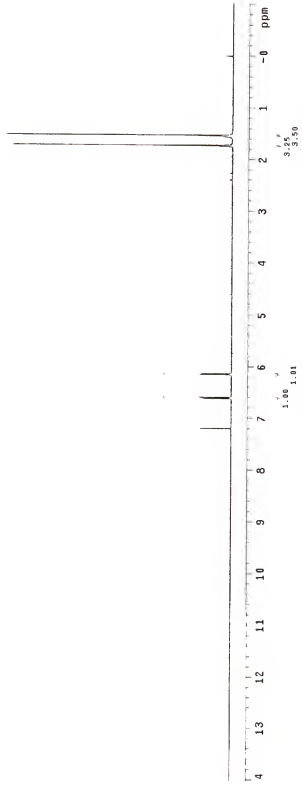

ppm
0
20
40
60
80
100
120
140
160
180
200
23.042
22.065
71.087
77.652
77.230
76.808
89.529
93.137
128.525
133.092
135.493
141.099

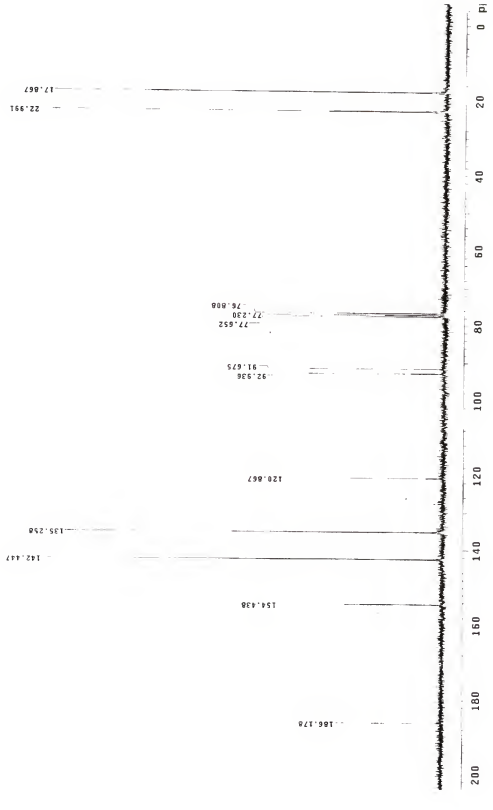
Br
Br
O
O


ppm
0
1
2
3
4
5
6
7
8
9
10
11
0.97
0.99
1.02
1.03

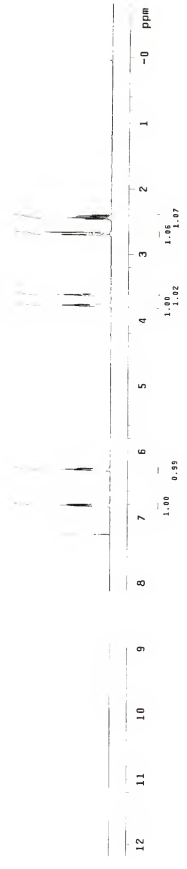

ppm
0
20
40
60
80
100
120
140
160
180
200
103.777
149.382
130.888
131.558
120.344
87.888
86.887
77.652
77.238
76.888

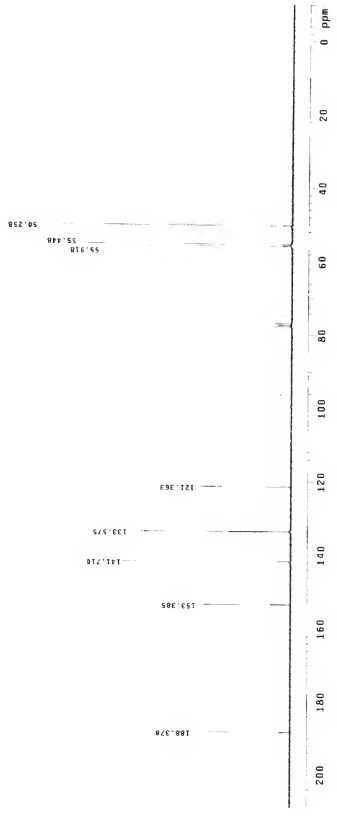
Br
Br
O
O

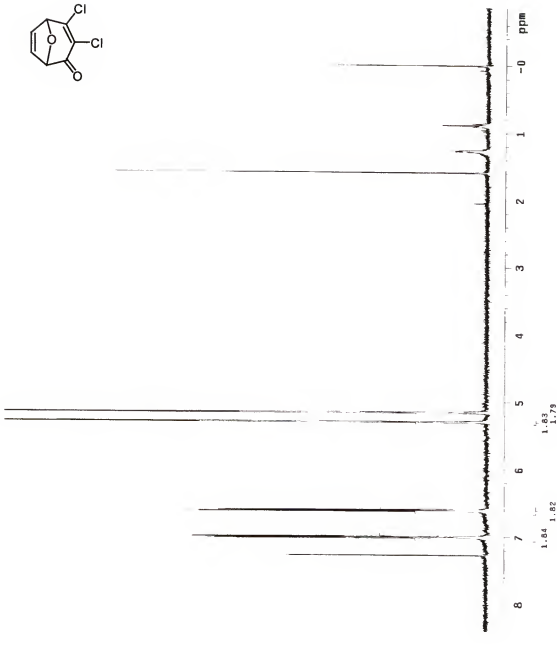

ppm
3.25
3.50
1.00
1.01

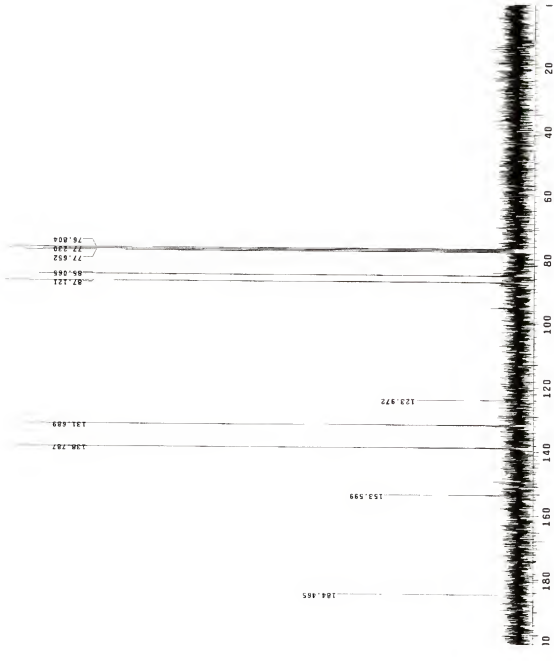

17.667
22.951
77.652
77.230
76.808
92.936
91.675
120.667
135.256
142.147
154.436
186.178
0
20
40
60
80
100
120
140
160
180
200
PI

Br
Br
O

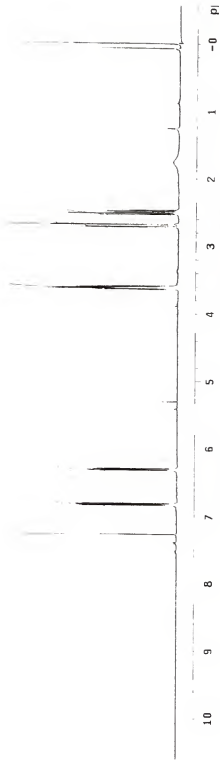

ppm
12
11
10
9
8
7
6
5
4
3
2
1
-0
1.00
0.99
1.00
1.02
1.06
1.07


188.378
153.385
141.710
133.575
121.363
55.448
55.018
50.258
0 ppm
20
40
60
80
100
120
140
160
180
200


Cl
Cl
O
O
ppm
8
7
6
5
4
3
2
1
0
1.84
1.82
1.83
1.79


164.165
153.599
138.787
131.689
123.972
82.121
78.044
77.652
77.230
76.804
85.065
200
180
160
140
120
100
80
60
40
20
0

Cl
Cl
O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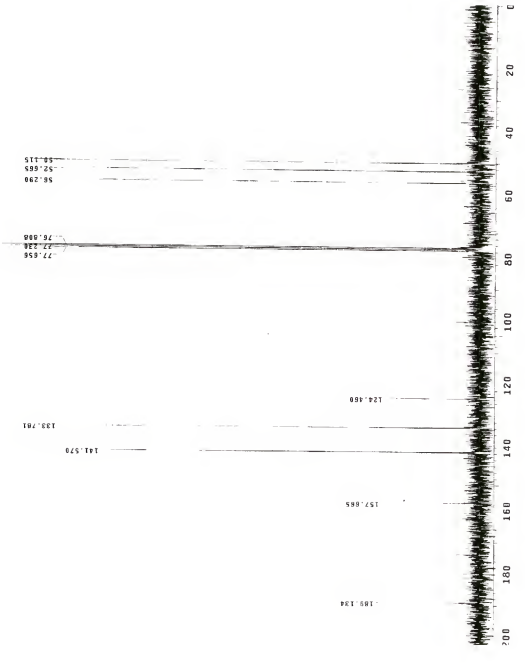
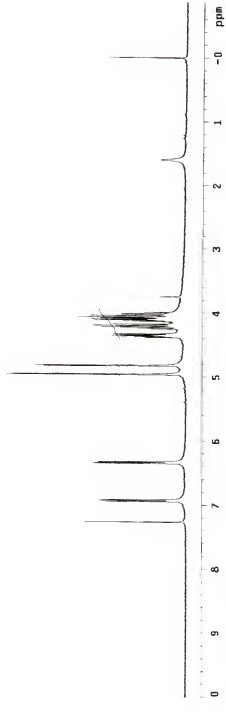
2
3
4
5
6
7
8
9
10
1.89
1.69
2.04
1.00
0.99


189.134
157.885
141.570
133.741
124.460
77.656
77.238
76.886
56.290
52.665
50.115
200
180
160
140
120
100
80
60
40
20
0

Br
Br
O
O
O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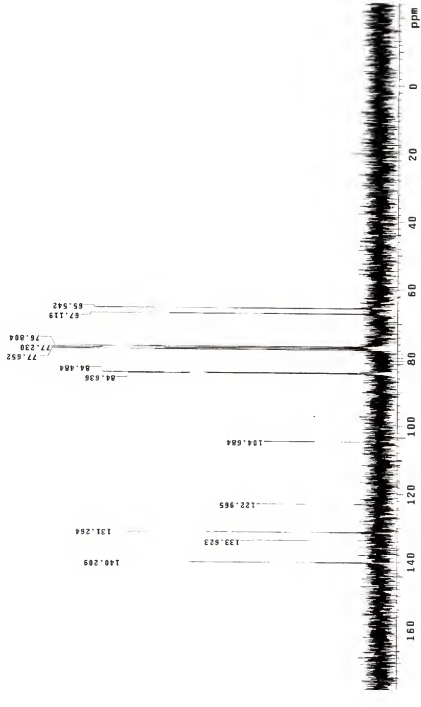
2
3
4
5
6
7
8
9
6.22
0.98
1.03
1.90
1.01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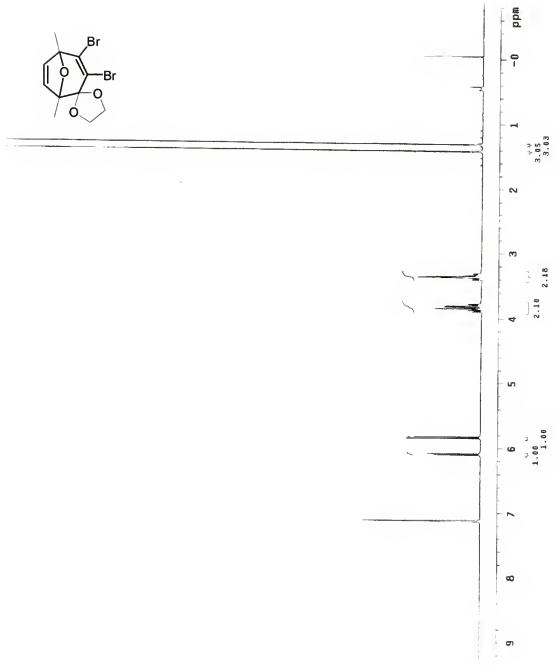
40
60
80
100
120
140
160
65.542
67.119
76.864
77.230
77.652
84.464
84.636
104.664
122.965
131.264
133.623
140.209


Br
Br
O
O
O
ppm
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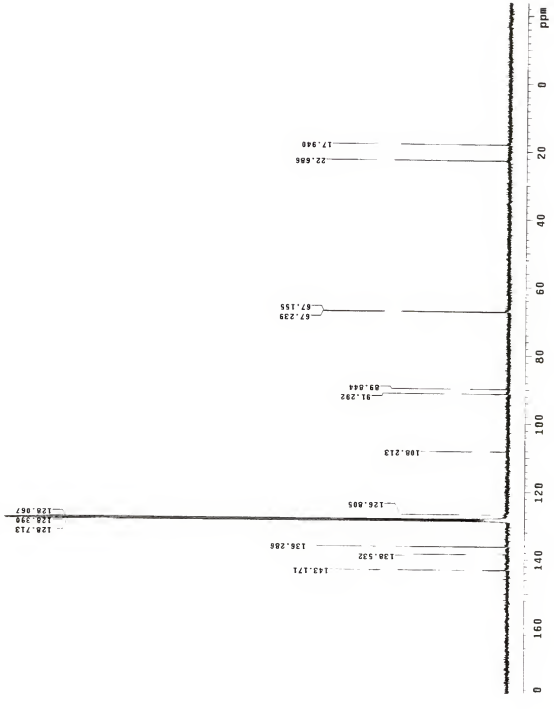
2
3
4
5
6
7
8
9
3.06
3.03
2.10
2.18
1.00
1.00


ppm
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40
60
80
100
120
140
160
17.940
22.686
67.239
67.155
89.644
91.292
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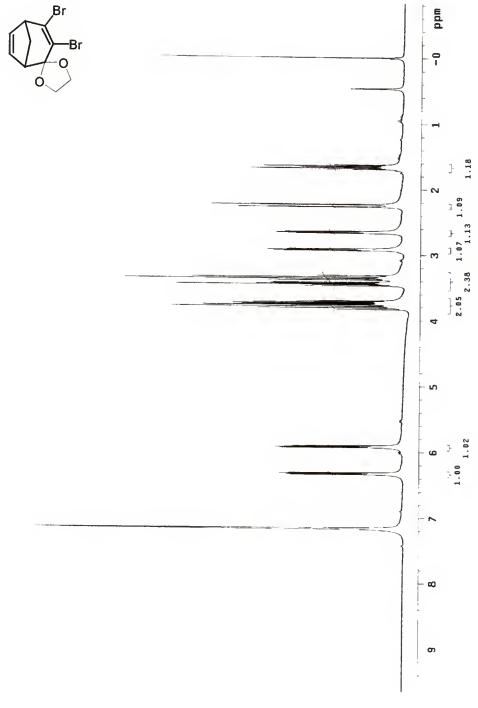
128.399
128.743
136.286
138.532
143.171


Br
Br
O
O
ppm
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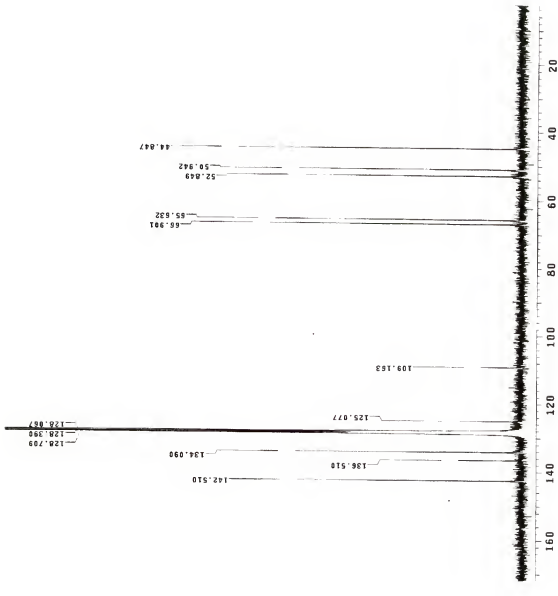
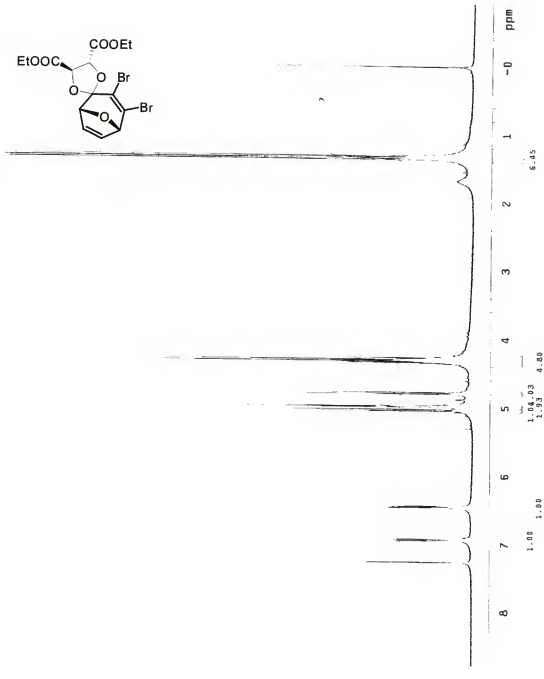
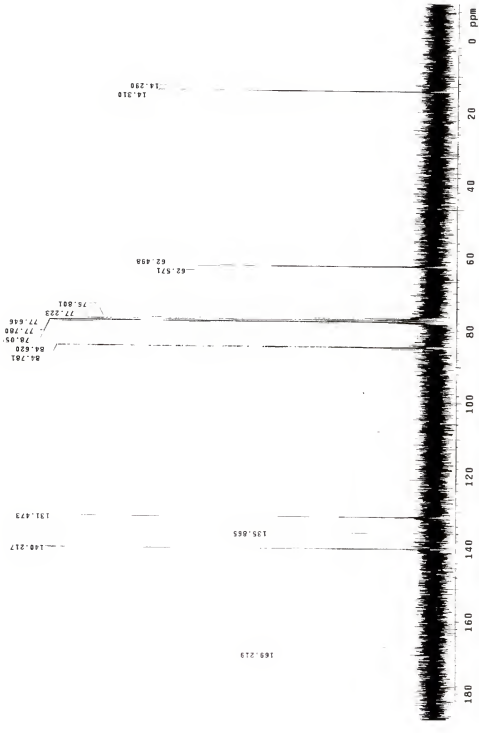
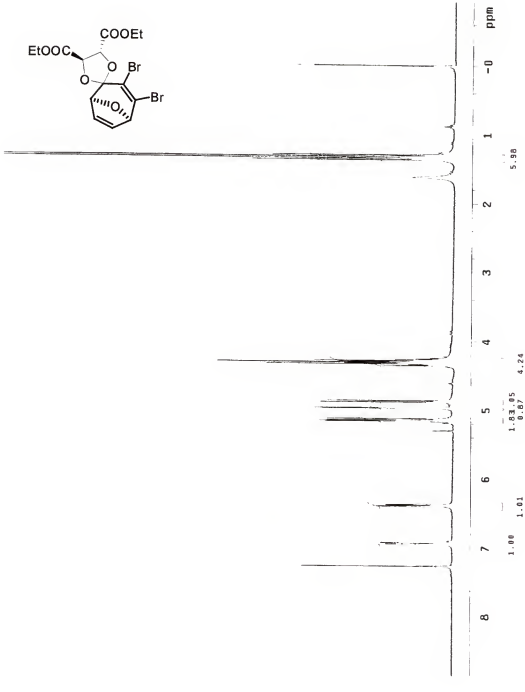
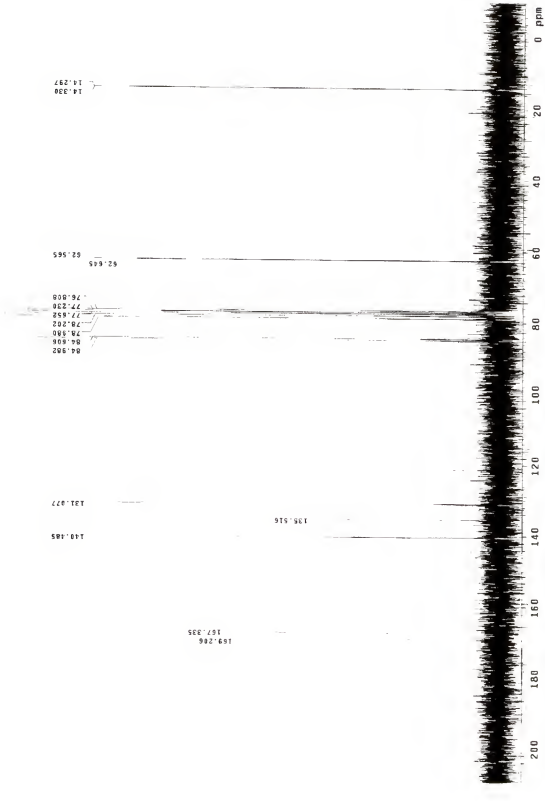
1.02
2.65
2.38
1.07
1.13
1.09
1.18

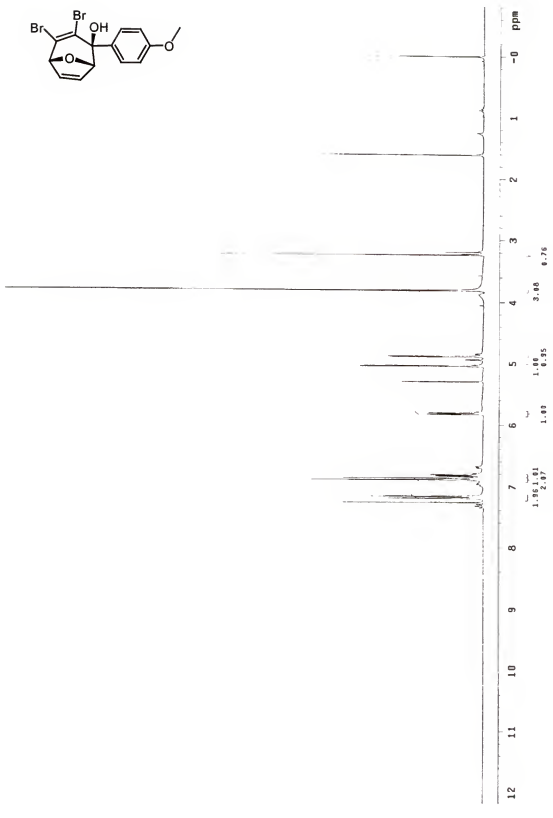

142.510
136.510
134.090
128.799
128.398
128.067
125.077
109.163
66.991
65.632
52.849
50.942
44.047
160
140
120
100
80
60
40
20

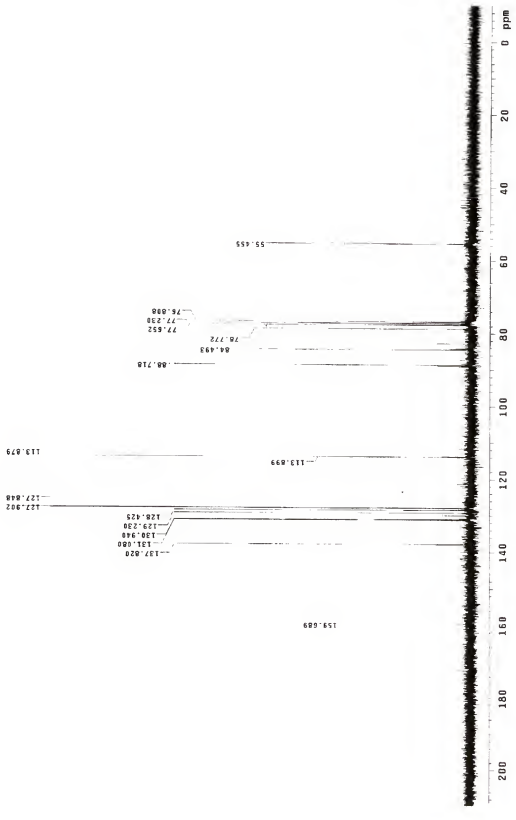

COOEt
EtOOC
O
Br
O
Br
O
ppm
-0
1
2
3
4
5
6
7
8
6.45
4.00
1.04
1.03
1.93
1.00
1.00

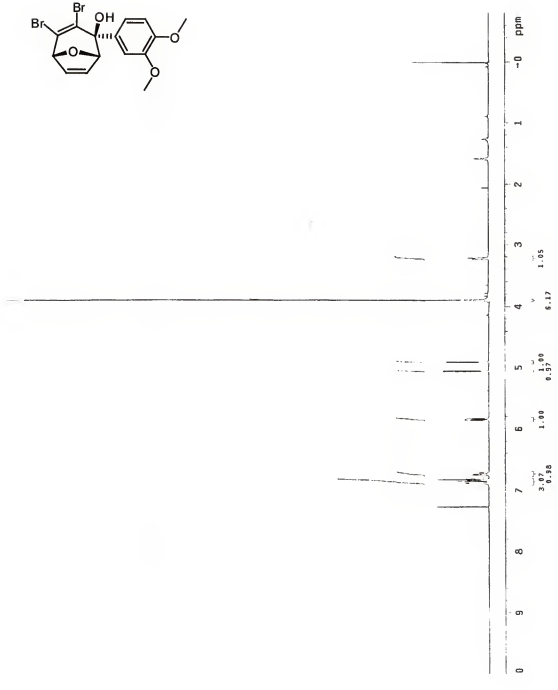

14.318
14.290
62.571
62.498
75.881
77.223
77.646
77.280
78.057
84.620
84.261
131.473
135.865
148.217
169.219
ppm
0
20
40
60
80
100
120
140
160
180

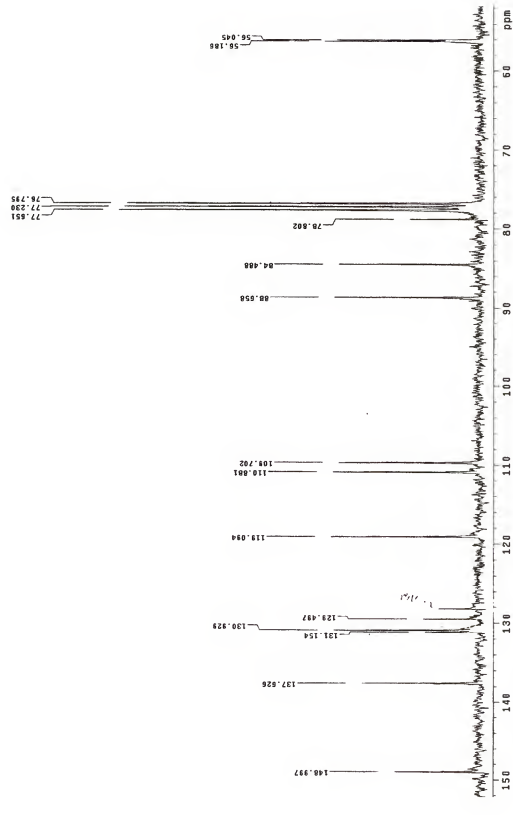

COOEt
EtOOC
O
Br
O
Br
O
ppm
0
1
2
3
4
5
6
7
8
5.98
4.24
1.03
0.87
1.00
1.01

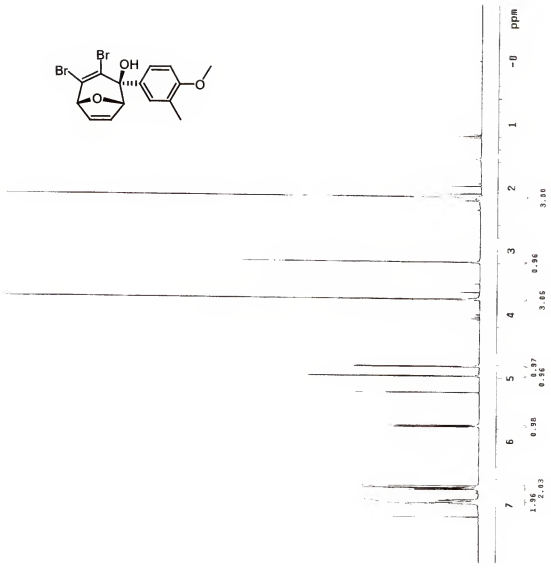

14.330
14.297
62.665
62.565
76.868
77.230
77.452
78.202
78.380
84.606
84.502
141.077
140.145
135.516
159.206
157.335
0 ppm
20
40
60
80
100
120
140
160
180
200

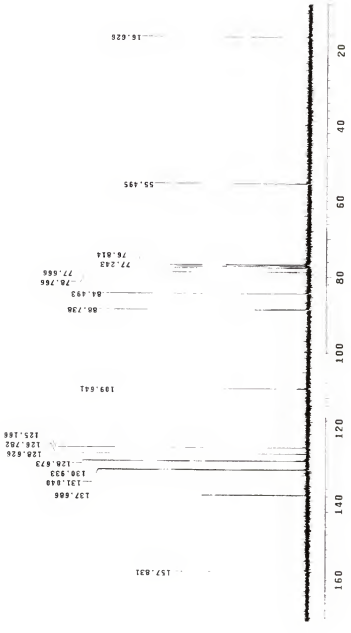

Br
Br
OH
O
O
ppm
0
1
2
3
4
5
6
7
8
9
10
11
12
6.76
3.00
1.00
0.95
1.03
1.01
2.97

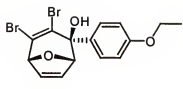

159.689
137.020
131.680
130.948
129.230
128.423
122.902
127.848
113.699
113.679
88.748
84.493
78.772
77.652
77.230
75.888
55.455
ppm
0
20
40
60
80
100
120
140
160
180
200

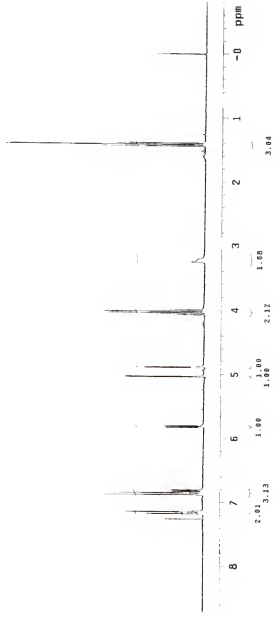

Br
OH
Br
O
O
O
ppm
0
1
2
3
4
5
6
7
8
9
3.07
1.00
1.00
0.97
6.17
1.05

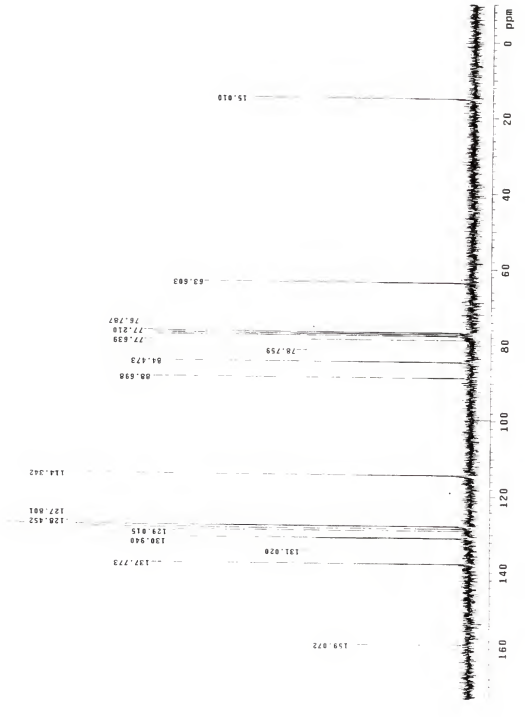

ppm
150
140
130
120
110
100
90
80
70
60
146.997
137.626
131.154
130.929
129.497
119.094
110.881
109.702
88.558
84.488
78.802
77.651
77.230
76.795
58.186
56.045


Br
Br
OH
O
O
ppm
0
1
2
3
4
5
6
7
3.00
0.96
3.66
0.97
0.96
0.98
1.96
2.03


157.831
137.686
131.040
130.933
126.673
128.626
126.762
125.166
109.641
86.736
84.193
78.766
77.666
77.243
76.814
55.495
16.626
160
140
120
100
80
60
40
20


Br
OH
Br
O
O


ppm
-0
1
2
3
4
5
6
7
8
3.04
1.68
2.12
1.00
1.00
1.00
2.01
3.13


ppm
0
20
40
60
80
100
120
140
160
15.010
63.603
76.787
77.210
77.639
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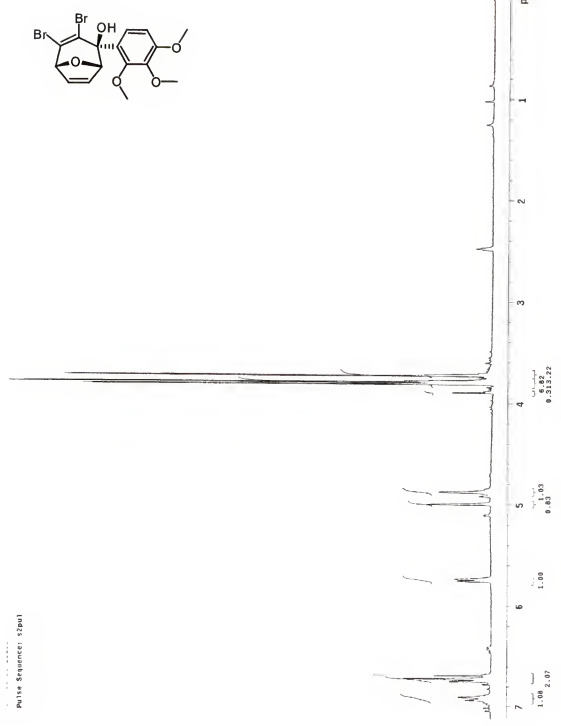
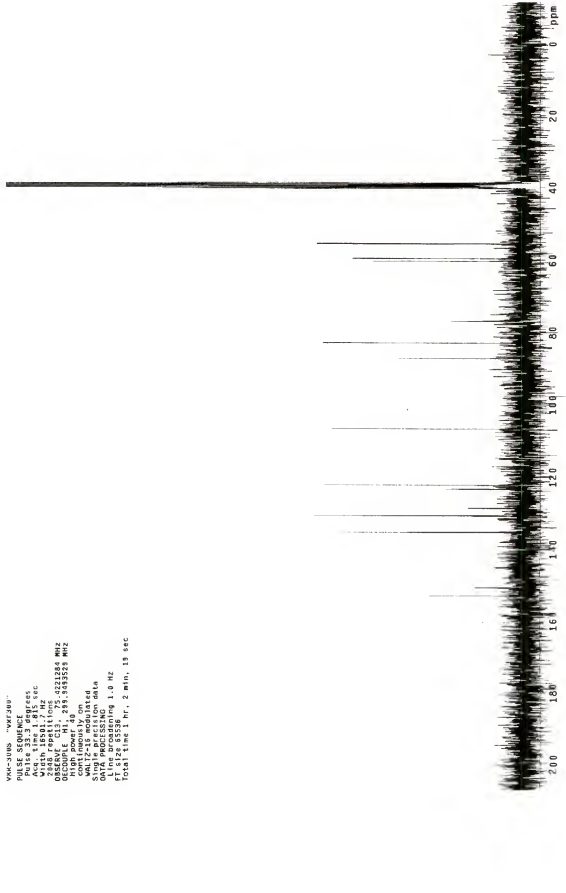
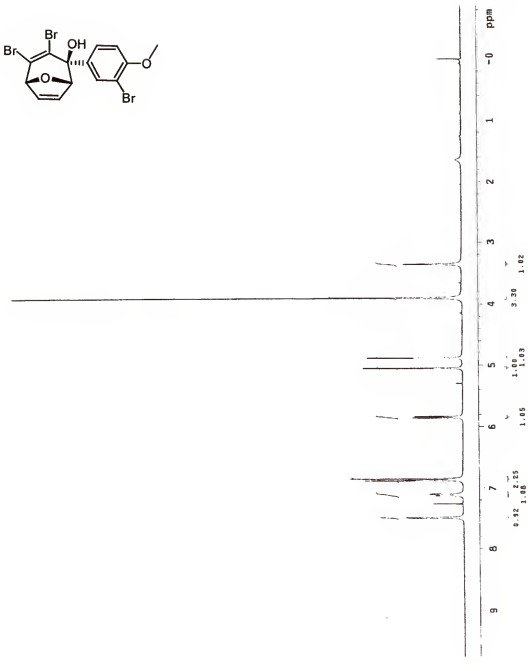
127.881
129.015
130.940
131.020
137.773
159.072


Br
OH
Br
O
O
O
O
Pulse Sequence: s2pul
ppm
1
2
3
4
5
6
7
1.00
0.83
25.22
2.07


VXR-300S "VXR300"
PULSE SEQUENCE
Relax. delay 1.000 sec
Pulse 73.3 degrees
Acq. time 1.820 sec
Width 16511.7 Hz
26000 points
OBSERVE C13, 75.4231284 MHz
DECOUPLE H1, 299.9450303 MHz
Power 38 dB
High power 40 dB
continuously on
WALTZ-16 modulated
Size 52000 data points
DATA PROCESSING
FT 32768
Exponential 1.0 Hz
Total time 1 hr, 2 min, 19 sec
200
180
160
140
120
100
80
60
40
20
0
ppm


Br
OH
Br
O
O
Br
ppm
0
1
2
3
4
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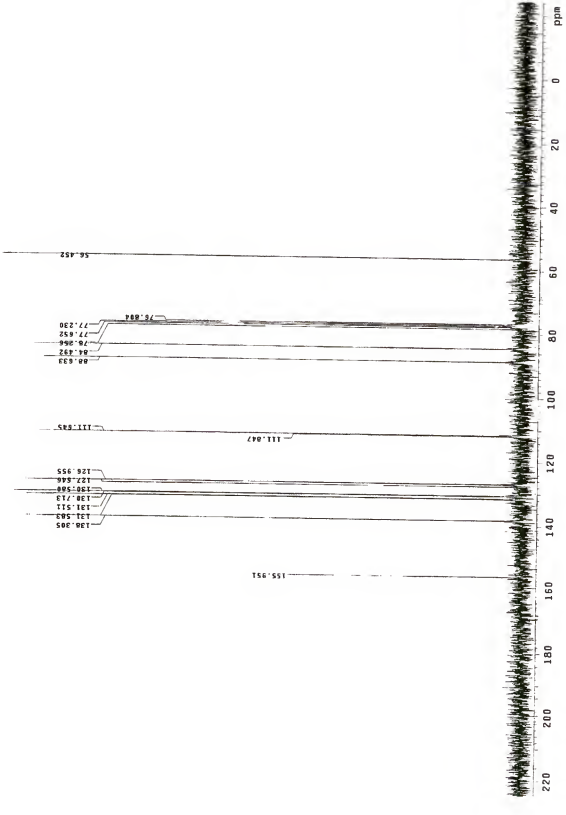
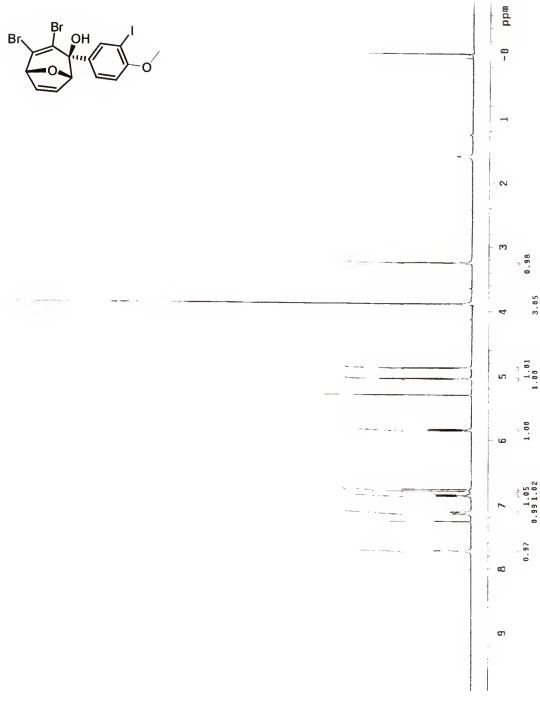
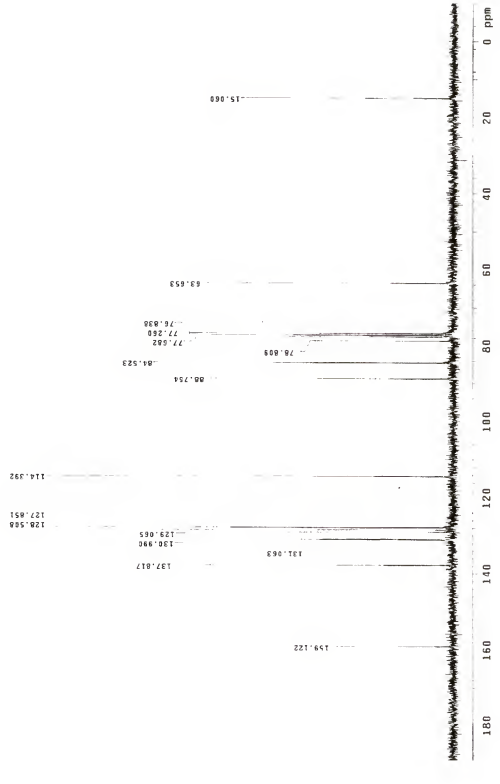
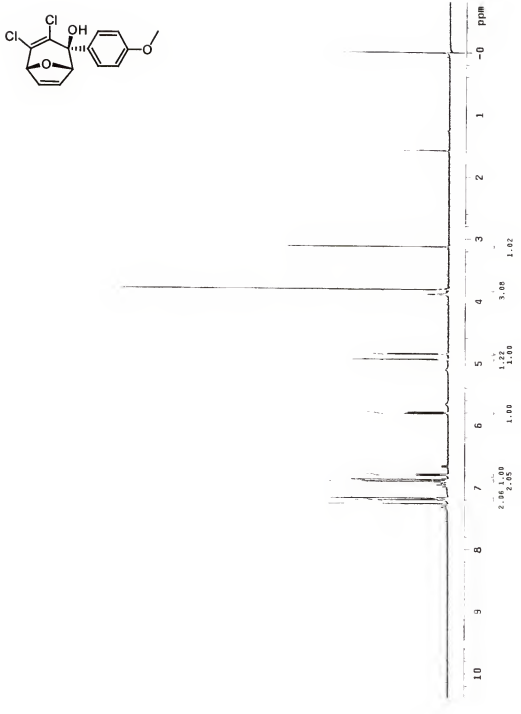
7
8
9
3.38
1.02
1.00
1.03
1.05
2.35
1.06
0.92


ppm
0
20
40
60
80
100
120
140
160
180
200
220
56.452
76.684
77.230
77.652
78.866
84.292
88.633
111.585
111.047
126.955
127.644
130.568
130.713
131.511
131.543
136.305
155.951


Br
Br
OH
I
O
O
ppm
9
8
7
6
5
4
3
2
1
0
0.97
1.05
0.93
1.02
1.00
1.01
1.00
3.05
0.98


ppm
0
20
40
60
80
100
120
140
160
180
15.060
63.653
77.682
77.268
76.836
76.699
84.523
88.754
114.392
120.568
127.651
129.065
130.990
131.063
137.817
159.122


Cl
OH
Cl
O
O
ppm
0
1
2
3
4
5
6
7
8
9
10
1.02
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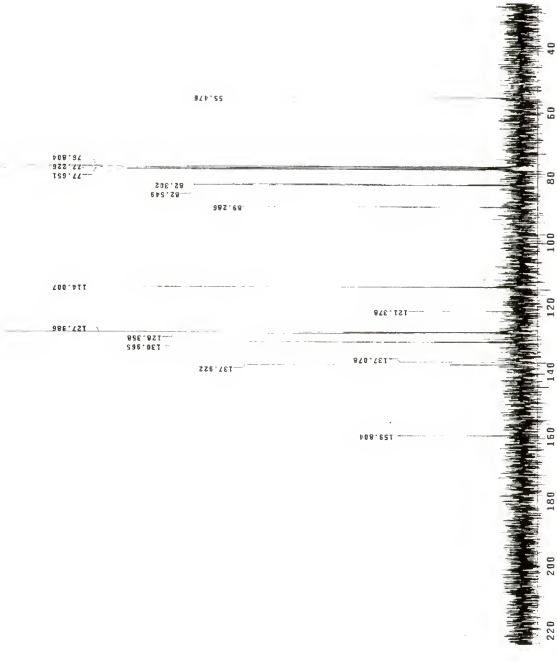
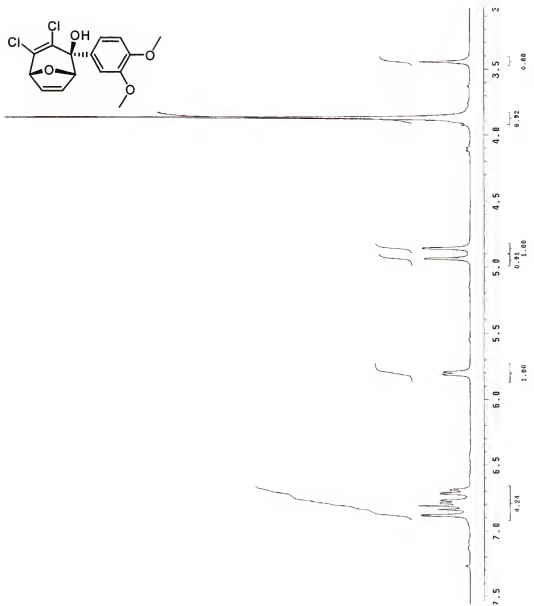
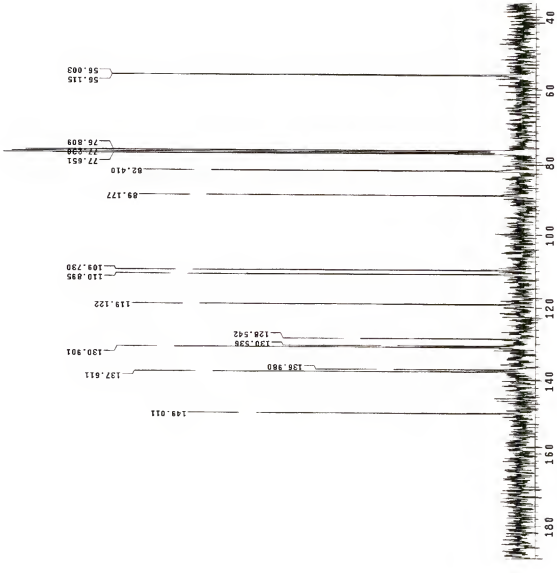
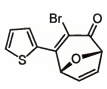
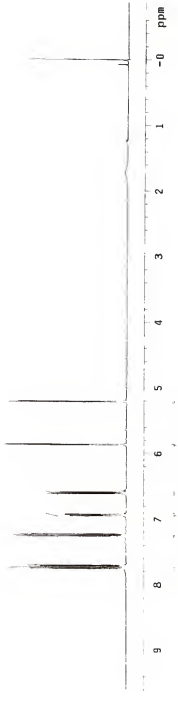
1.22
1.00
1.00
2.96
1.00
2.05

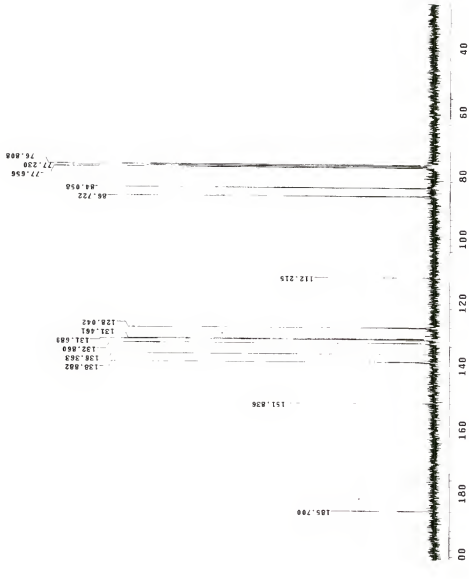

159.884
137.922
137.078
130.965
128.358
127.386
121.378
114.007
89.286
82.562
82.549
77.051
77.226
76.864
55.478
220
200
180
160
140
120
100
80
60
40

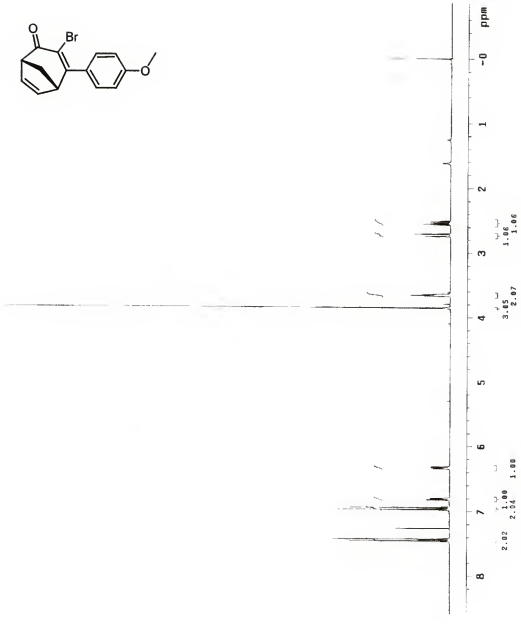

Cl
OH
Cl
O
O
O
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
4.84
1.00
1.00
0.91
1.00
0.92
6.80

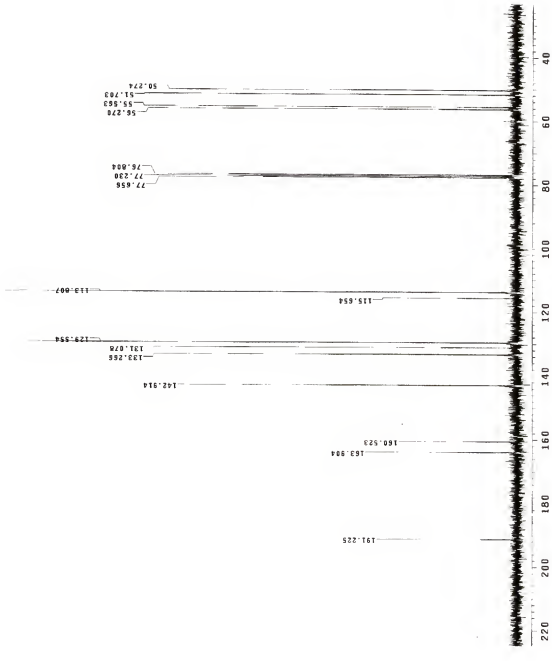

149.011
137.611
136.980
130.901
130.539
128.542
119.122
110.095
109.780
89.177
82.410
77.651
76.809
56.115
56.003
40
60
80
100
120
140
160
180

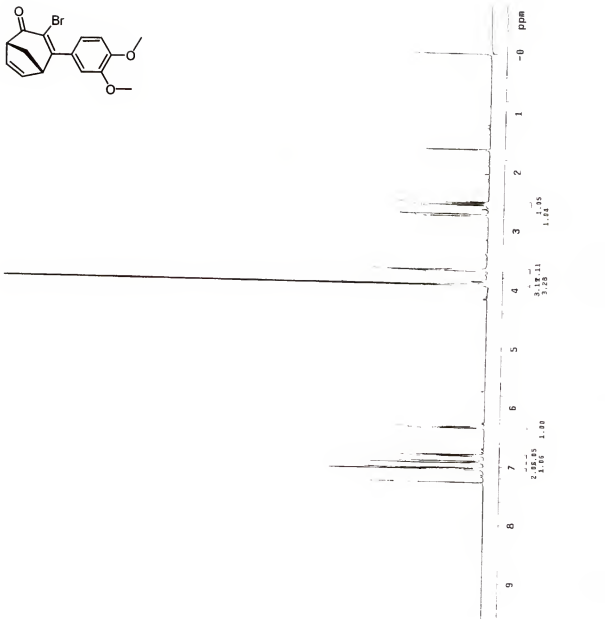

Br
O
S
O

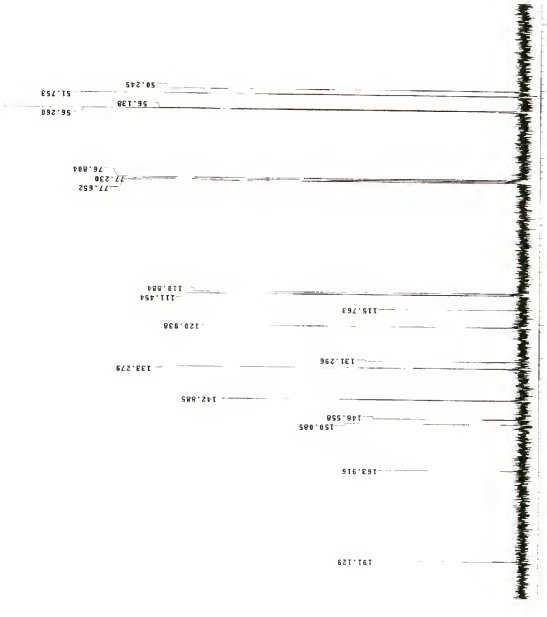

ppm
-0
1
2
3
4
5
6
7
8
9
2.02
1.26
1.02
1.00
0.97
0.94

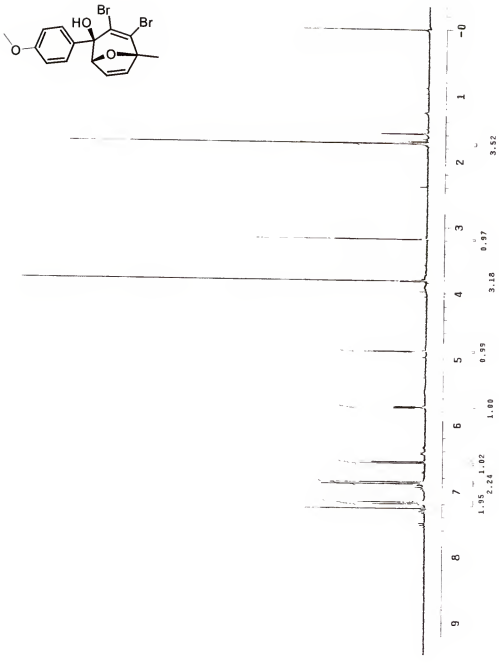

76.808
77.136
77.456
84.056
86.722
112.215
128.062
131.461
131.689
132.060
136.263
136.882
151.836
165.700
00
20
40
60
80
100
120
140
160
180

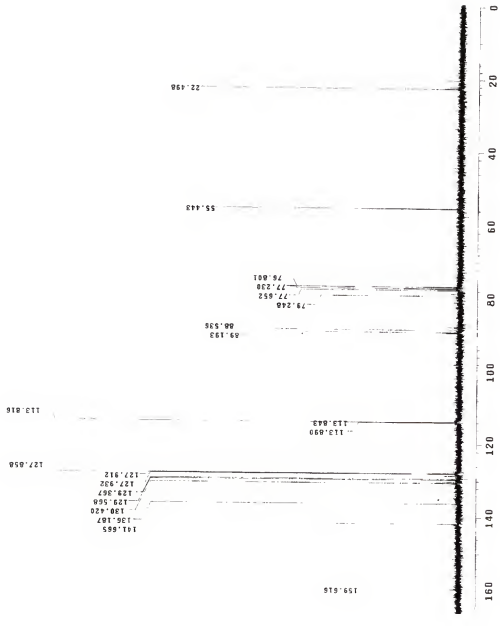

O
Br
O
ppm
8
7
6
5
4
3
2
1
0
2.02
1.00
2.54
1.88
3.65
2.07
1.05
1.06


50.274
51.703
55.563
56.278
76.604
77.230
77.656
113.007
115.654
129.554
131.678
133.255
142.914
160.523
163.984
191.225
40
60
80
100
120
140
160
180
200
220

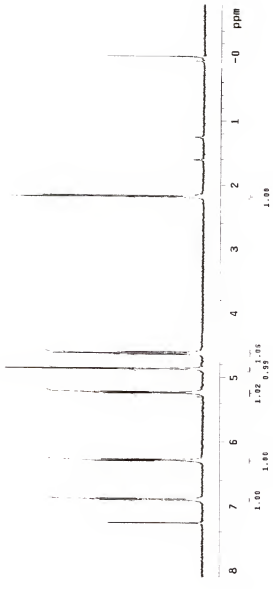

O
Br
O
O
ppm
0
1
2
3
4
5
6
7
8
9
3.11
3.28
1.35
1.84
2.16.85
1.00
1.00

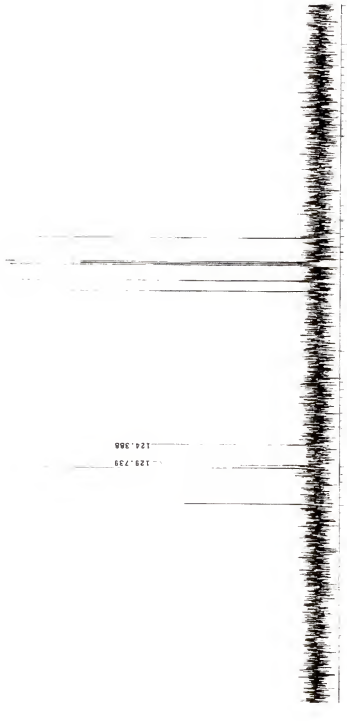

191.129
153.915
150.005
146.550
142.885
133.279
131.296
120.938
115.763
111.454
110.884
77.652
77.230
76.804
56.260
56.138
51.753
50.245
200
180
160
140
120
100
80
60
40

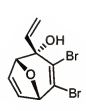

HO
Br
Br
O
O
3.82
0.97
3.18
0.99
1.00
1.02
2.24
1.95

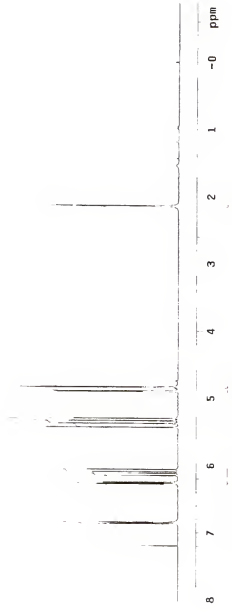

22.498
55.443
76.801
77.238
77.652
79.248
89.193
88.536
112.816
113.090
113.843
127.658
127.912
127.902
129.367
129.566
130.420
136.187
141.665
159.616
0
20
40
60
80
100
120
140
160

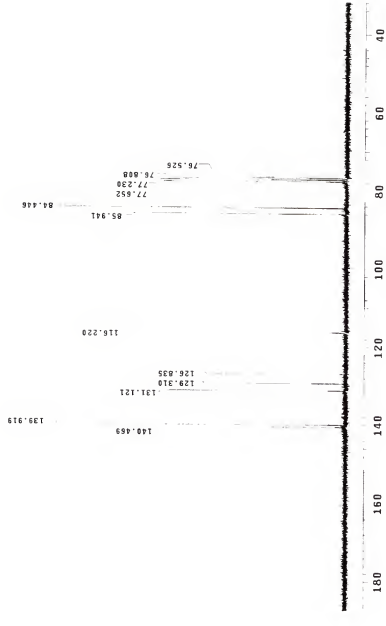
H
OH
Br
O
Br

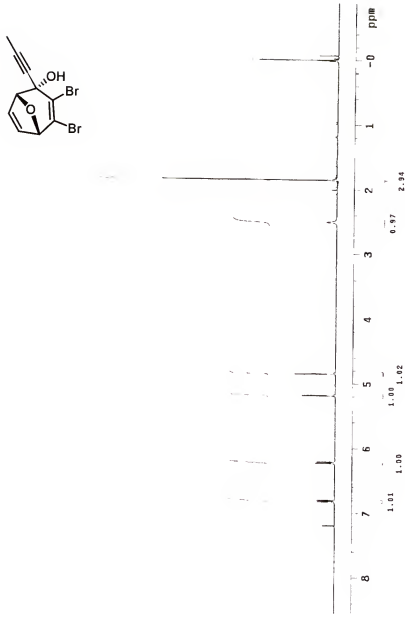

ppm
1.00
1.00
1.02
0.98
1.00


124.388
129.739
20
40
60
80
100
120
140
160
180


OH
Br
Br
O


8
7
6
5
4
3
2
1
-0
ppm
1.00
1.03
1.02
2.11
0.97
0.95


76.526
76.808
77.230
77.652
84.446
85.941
116.220
126.835
129.340
131.121
139.919
140.469
40
60
80
100
120
140
160
180


OH
Br
Br
O
ppm
0
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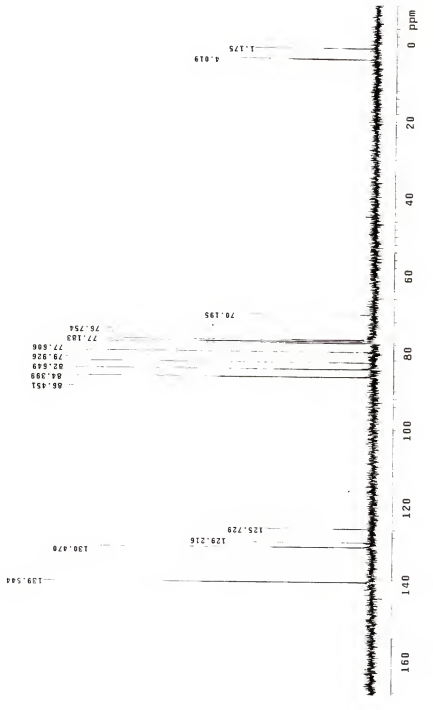
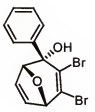
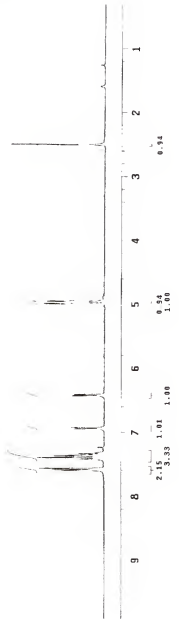
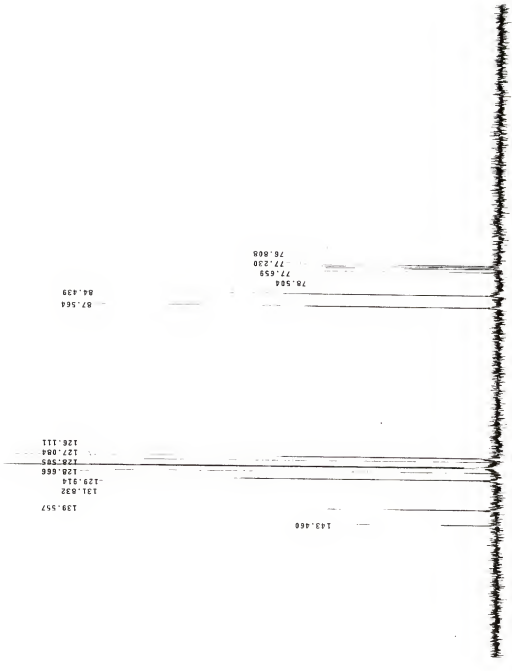
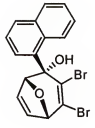
2
3
4
5
6
7
8
2.94
0.97
1.02
1.00
1.01
1.00

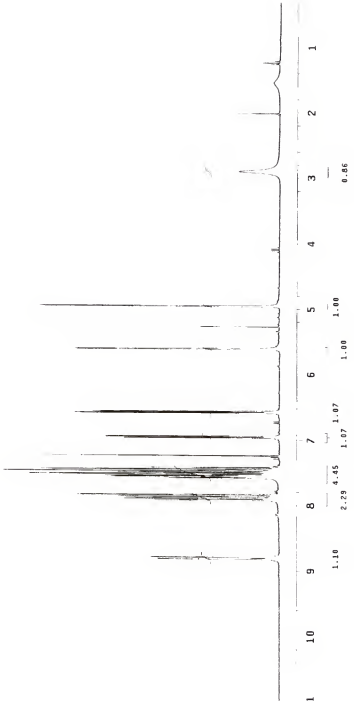

1.175
4.019
70.195
76.754
77.183
77.686
78.926
82.569
84.399
86.451
125.729
129.216
130.478
139.544
0 ppm
20
40
60
80
100
120
140
160

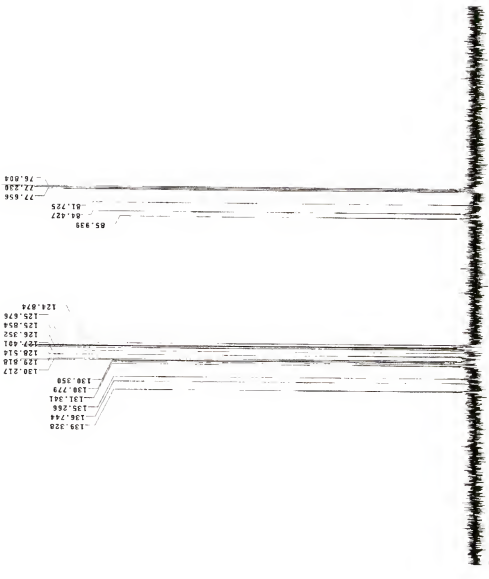

OH
Br
Br
O

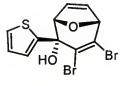

9
8
7
6
5
4
3
2
1
2.15
3.33
1.01
1.00
0.94
1.00
0.94

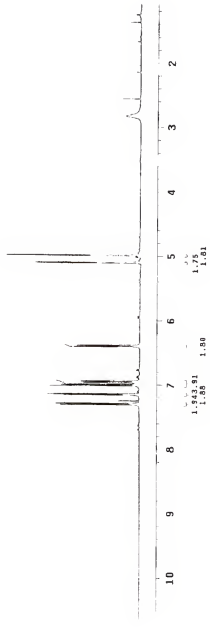

143.466
139.557
131.632
129.914
128.666
128.585
127.084
126.111
87.564
84.439
78.584
77.659
77.230
76.808
20
40
60
80
100
120
140
160

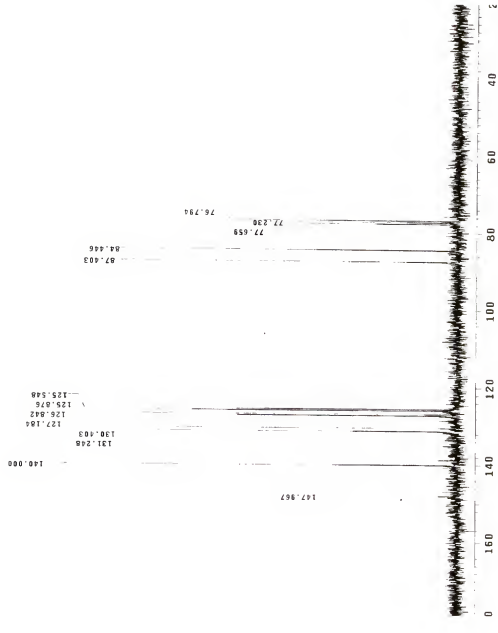

OH
Br
Br
O

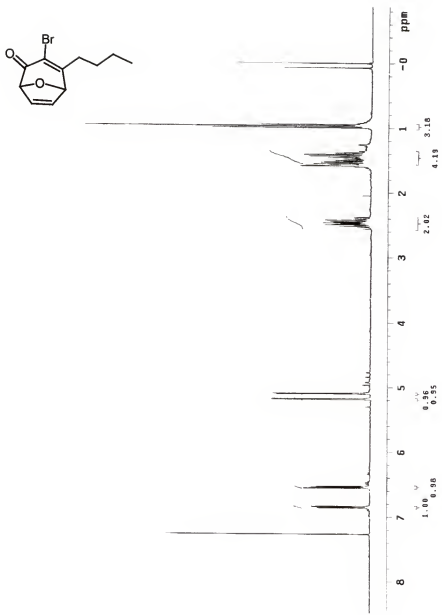

10
9
8
7
6
5
4
3
2
1
1.10
2.29
4.45
1.07
1.07
1.00
1.00
0.86

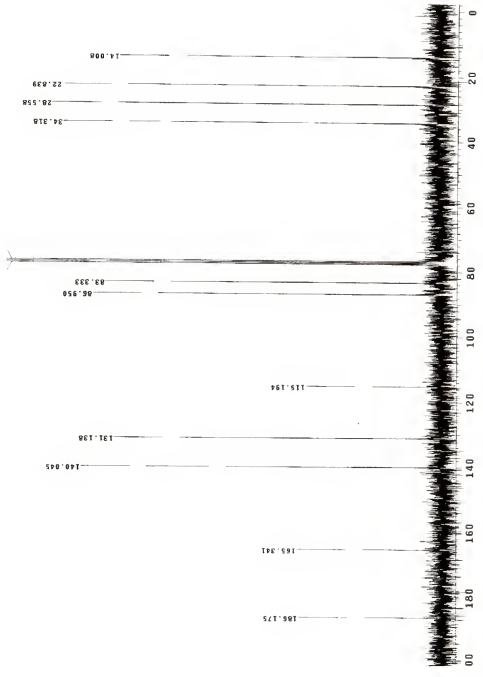

76.604
77.238
77.656
81.725
84.427
85.939
124.874
125.676
129.054
126.352
127.491
120.514
123.618
130.217
130.559
130.779
131.341
135.266
136.744
139.328
2
40
60
80
100
120
140
160
180

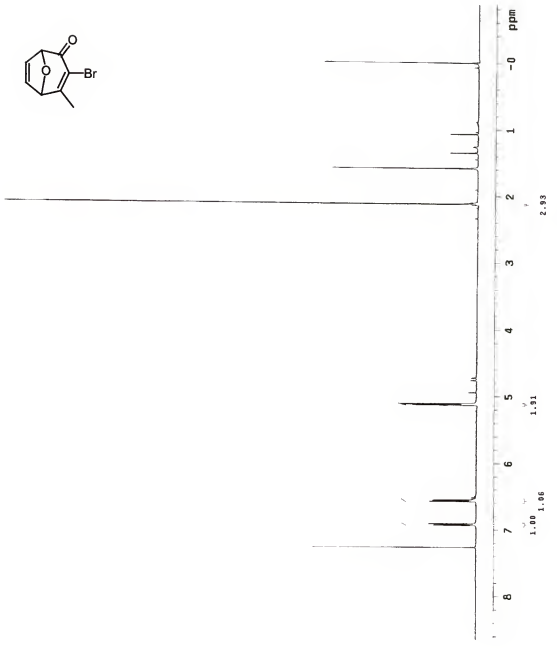

S
O
HO
Br
Br

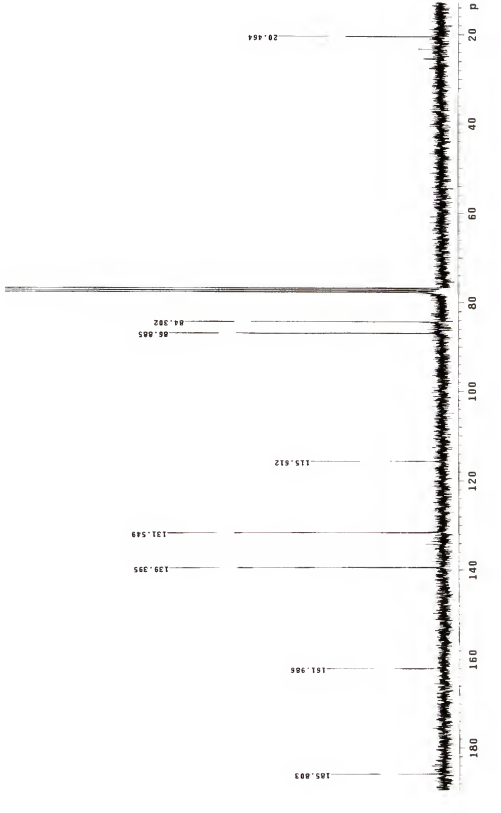

2
3
4
5
6
7
8
9
10
1.79
1.81
1.80
1.84
1.86


147.967
140.000
131.248
130.403
127.186
126.842
125.876
125.548
87.403
84.446
77.659
77.238
76.794
0
20
40
60
80
100
120
140
160


Br
O
O
ppm
0
1
2
3
4
5
6
7
8
3.16
4.19
2.02
8.56
0.55
1.00
0.98


14.008
22.839
26.556
34.318
83.333
86.950
115.194
131.136
140.045
165.341
166.175
0
20
40
60
80
100
120
140
160
180
200


O
O
Br
ppm
-0
1
2
3
4
5
6
7
8
2.93
1.91
1.00
1.86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85.885
115.612
131.549
139.395
161.966
185.003
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60
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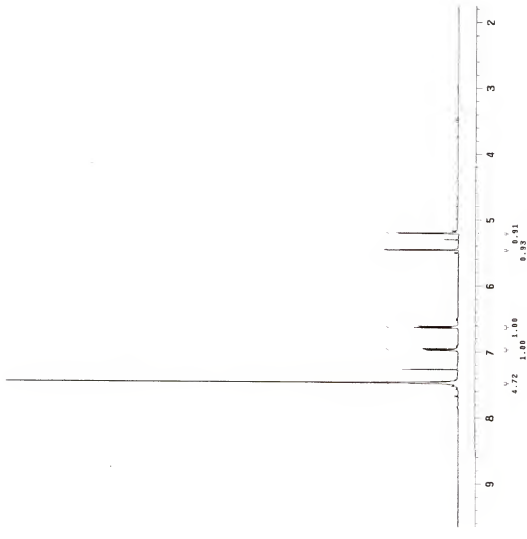
140
160
180
p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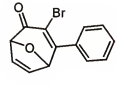
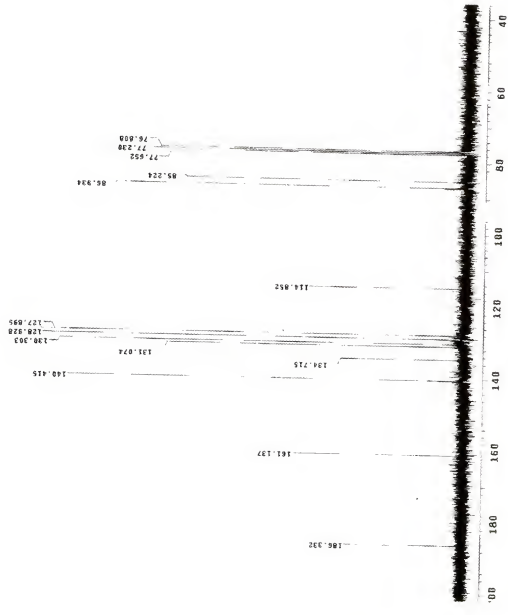
0.91


O
Br
O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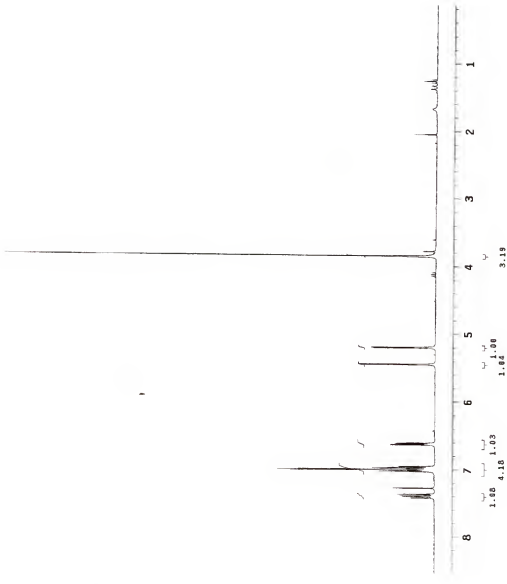
60
80
100
120
140
160
180
200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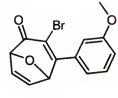
1.03
1.00
1.04
3.19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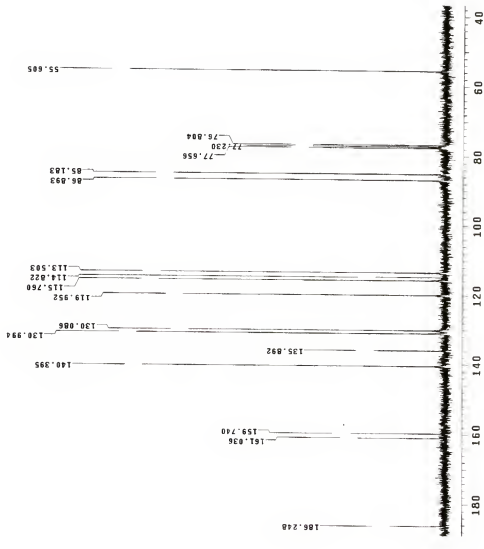
Br
O
O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130.086
130.994
119.952
115.760
114.022
113.503
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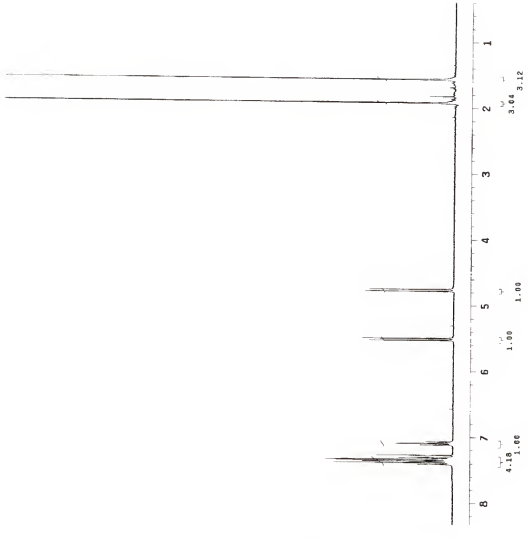
55.605
180
160
140
120
100
80
60
40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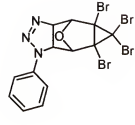
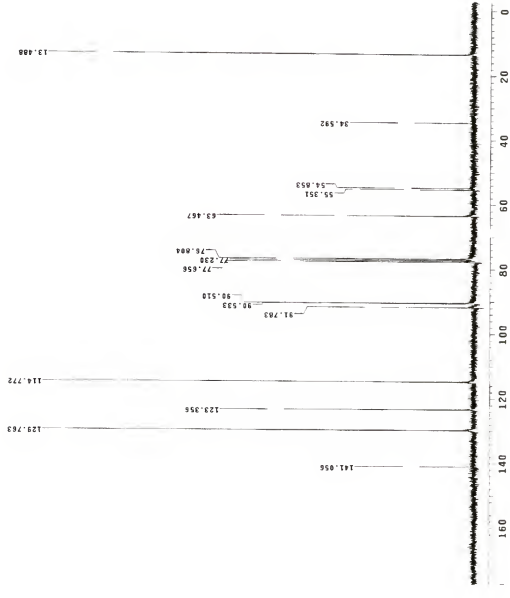
2
3
4
5
6
7
8
3.04
3.12
1.00
1.00
4.18
1.00


Br
Br
Br
Br
N
N
N
O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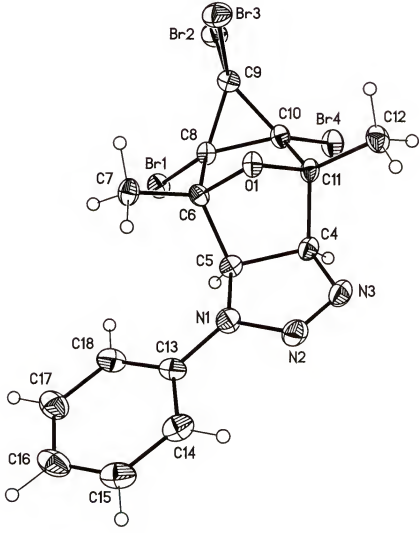
55.351
63.467
76.804
77.238
77.656
90.510
90.533
91.703
114.772
123.356
129.763
141.056
0
20
40
60
80
100
120
140
160

APPENDIX C
X-RAY CRYSTALLOGRAPHIC DATA

X-Ray data for **90**



**X-ray experimental for 90**: Data were collected at 173 K on a Siemens SMART PLATFORM equipped with A CCD area detector and a graphite monochromator utilizing $MoK_\alpha$ radiation ($\lambda = 0.71073$ Å). Cell parameters were refined using up to 8192 reflections. A full sphere of data (1850 frames) was collected using the $\omega$-scan method (0.3° frame width). The first 50 frames were remeasured at the end of data collection to monitor instrument and crystal stability (maximum correction on I was < 1 %). Absorption corrections by integration were applied based on measured indexed crystal faces.

The structure was solved by the Direct Methods in *SHELXTL5,* and refined using full-matrix least squares. The non-H atoms were treated anisotropically, whereas the hydrogen atoms were calculated in ideal positions and were riding on their respective carbon atoms. A total of 210 parameters were refined in the final cycle of refinement using 14873 reflections with $I > 2\sigma(I)$ to yield $R_1$ and $wR_2$ of 2.45% and 6.27%, respectively. Refinement was done using $F^2$.

Sheldrick, G. M. (1998). *SHELXTL5*. Bruker-AXS, Madison, Wisconsin, USA.

Table 1. Crystal data and structure refinement for **90**.

| | | |
|---|---|---|
| Identification code | ro09 | |
| Empirical formula | C15 H13 Br4 N3 O | |
| Formula weight | 570.92 | |
| Temperature | 173(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Monoclinic | |
| Space group | P2(1)/n | |
| Unit cell dimensions | a = 7.2819(4) Å | α= 90°. |
| | b = 14.1493(8) Å | β= 90.188(2)°. |
| | c = 16.561(2) Å | γ = 90°. |
| Volume | 1706.32(17) $Å^3$ | |
| Z | 4 | |
| Density (calculated) | 2.222 $Mg/m^3$ | |
| Absorption coefficient | 9.441 $mm^{-1}$ | |

| | |
|---|---|
| F(000) | 1088 |
| Crystal size | 0.24 x 0.19 x 0.05 $mm^3$ |
| Theta range for data collection | 1.89 to 27.50°. |
| Index ranges | $-9 \le h \le 9$, $-18 \le k \le 18$, $-21 \le l \le 21$ |
| Reflections collected | 14873 |
| Independent reflections | 3901 [R(int) = 0.0554] |
| Completeness to theta = 27.50° | 99.4 % |
| Absorption correction | Integration |
| Max. and min. transmission | 0.6269 and 0.1457 |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | 3901 / 0 / 210 |
| Goodness-of-fit on $F^2$ | 0.987 |
| Final R indices [I>2sigma(I)] | R1 = 0.0245, wR2 = 0.0627 [3303] |
| R indices (all data) | R1 = 0.0315, wR2 = 0.0645 |
| Largest diff. peak and hole | 0.508 and -0.634 e.$Å^{-3}$ |

$R1 = \Sigma(||F_o| - |F_c||) / \Sigma|F_o|$

$wR2 = [\Sigma[w(F_o^2 - F_c^2)^2] / \Sigma[w(F_o^2)^2]]^{1/2}$

$S = [\Sigma[w(F_o^2 - F_c^2)^2] / (n-p)]^{1/2}$

$w = 1/[\sigma^2(F_o^2)+(m*p)^2+n*p]$, $p = [\max(F_o^2,0)+ 2* F_c^2]/3$, m & n are constants.

Table 2. Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters ($Å^2$x $10^3$) for 90. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| Br1 | 1547(1) | 1126(1) | 7287(1) | 23(1) |
| Br2 | 2130(1) | 1257(1) | 9297(1) | 27(1) |
| Br3 | 3311(1) | -850(1) | 9383(1) | 29(1) |
| Br4 | 6002(1) | 1817(1) | 8305(1) | 26(1) |
| O1 | 5198(2) | -996(1) | 7815(1) | 18(1) |
| N1 | 5438(3) | -915(2) | 6030(1) | 23(1) |
| N2 | 7297(3) | -1079(2) | 6098(2) | 26(1) |
| N3 | 8040(3) | -574(2) | 6622(1) | 25(1) |
| C4 | 6694(3) | 70(2) | 7003(2) | 19(1) |
| C5 | 4836(3) | -196(2) | 6596(2) | 18(1) |

| | | | | |
|---|---|---|---|---|
| C6 | 3750(3) | -595(2) | 7330(2) | 16(1) |
| C7 | 2290(3) | -1331(2) | 7195(2) | 21(1) |
| C8 | 3202(3) | 295(2) | 7822(2) | 16(1) |
| C9 | 3387(3) | 280(2) | 8727(2) | 19(1) |
| C10 | 5021(3) | 575(2) | 8221(2) | 19(1) |
| C11 | 6362(3) | -175(2) | 7898(2) | 17(1) |
| C12 | 8017(4) | -387(2) | 8417(2) | 24(1) |
| C13 | 4453(4) | -1279(2) | 5370(2) | 22(1) |
| C14 | 5266(4) | -1922(2) | 4845(2) | 27(1) |
| C15 | 4234(4) | -2305(2) | 4223(2) | 31(1) |
| C16 | 2393(5) | -2082(2) | 4116(2) | 32(1) |
| C17 | 1612(4) | -1428(2) | 4634(2) | 31(1) |
| C18 | 2618(4) | -1016(2) | 5252(2) | 27(1) |

Table 3. Bond lengths [Å] and angles [°] for **90**.

| | |
|---|---|
| Br1-C8 | 1.901(2) |
| Br2-C9 | 1.909(3) |
| Br3-C9 | 1.934(3) |
| Br4-C10 | 1.902(3) |
| O1-C6 | 1.440(3) |
| O1-C11 | 1.443(3) |
| N1-N2 | 1.378(3) |
| N1-C13 | 1.403(3) |
| N1-C5 | 1.452(3) |
| N2-N3 | 1.247(3) |
| N3-C4 | 1.481(3) |
| C4-C11 | 1.542(4) |
| C4-C5 | 1.556(3) |
| C4-H4A | 1.0000 |
| C5-C6 | 1.558(3) |
| C5-H5A | 1.0000 |
| C6-C7 | 1.504(3) |
| C6-C8 | 1.553(3) |
| C7-H7A | 0.9800 |

| | |
|---|---|
| C7-H7B | 0.9800 |
| C7-H7C | 0.9800 |
| C8-C9 | 1.505(4) |
| C8-C10 | 1.530(3) |
| C9-C10 | 1.517(4) |
| C10-C11 | 1.540(3) |
| C11-C12 | 1.507(3) |
| C12-H12A | 0.9800 |
| C12-H12B | 0.9800 |
| C12-H12C | 0.9800 |
| C13-C14 | 1.393(4) |
| C13-C18 | 1.400(4) |
| C14-C15 | 1.383(4) |
| C14-H14A | 0.9500 |
| C15-C16 | 1.388(5) |
| C15-H15A | 0.9500 |
| C16-C17 | 1.386(4) |
| C16-H16A | 0.9500 |
| C17-C18 | 1.385(4) |
| C17-H17A | 0.9500 |
| C18-H18A | 0.9500 |

| | |
|---|---|
| C6-O1-C11 | 99.52(17) |
| N2-N1-C13 | 120.1(2) |
| N2-N1-C5 | 111.3(2) |
| C13-N1-C5 | 127.3(2) |
| N3-N2-N1 | 112.6(2) |
| N2-N3-C4 | 111.3(2) |
| N3-C4-C11 | 112.2(2) |
| N3-C4-C5 | 104.0(2) |
| C11-C4-C5 | 102.91(19) |
| N3-C4-H4A | 112.3 |
| C11-C4-H4A | 112.3 |
| C5-C4-H4A | 112.3 |
| N1-C5-C4 | 100.70(19) |
| N1-C5-C6 | 113.8(2) |

| | |
|---|---|
| C4-C5-C6 | 101.1(2) |
| N1-C5-H5A | 113.3 |
| C4-C5-H5A | 113.3 |
| C6-C5-H5A | 113.3 |
| O1-C6-C7 | 109.0(2) |
| O1-C6-C8 | 102.42(18) |
| C7-C6-C8 | 117.1(2) |
| O1-C6-C5 | 101.86(18) |
| C7-C6-C5 | 119.7(2) |
| C8-C6-C5 | 104.3(2) |
| C6-C7-H7A | 109.5 |
| C6-C7-H7B | 109.5 |
| H7A-C7-H7B | 109.5 |
| C6-C7-H7C | 109.5 |
| H7A-C7-H7C | 109.5 |
| H7B-C7-H7C | 109.5 |
| C9-C8-C10 | 59.95(16) |
| C9-C8-C6 | 119.3(2) |
| C10-C8-C6 | 102.33(19) |
| C9-C8-Br1 | 121.80(17) |
| C10-C8-Br1 | 125.94(17) |
| C6-C8-Br1 | 114.92(17) |
| C8-C9-C10 | 60.86(16) |
| C8-C9-Br2 | 116.16(17) |
| C10-C9-Br2 | 116.86(17) |
| C8-C9-Br3 | 124.68(17) |
| C10-C9-Br3 | 124.26(17) |
| Br2-C9-Br3 | 107.80(13) |
| C9-C10-C8 | 59.19(16) |
| C9-C10-C11 | 120.1(2) |
| C8-C10-C11 | 102.71(19) |
| C9-C10-Br4 | 120.65(18) |
| C8-C10-Br4 | 126.57(17) |
| C11-C10-Br4 | 115.11(16) |
| O1-C11-C12 | 111.3(2) |
| O1-C11-C10 | 102.42(18) |

| | |
|---|---|
| C12-C11-C10 | 116.5(2) |
| O1-C11-C4 | 100.6(2) |
| C12-C11-C4 | 117.7(2) |
| C10-C11-C4 | 106.2(2) |
| C11-C12-H12A | 109.5 |
| C11-C12-H12B | 109.5 |
| H12A-C12-H12B | 109.5 |
| C11-C12-H12C | 109.5 |
| H12A-C12-H12C | 109.5 |
| H12B-C12-H12C | 109.5 |
| C14-C13-C18 | 119.6(3) |
| C14-C13-N1 | 120.6(2) |
| C18-C13-N1 | 119.8(2) |
| C15-C14-C13 | 119.3(3) |
| C15-C14-H14A | 120.3 |
| C13-C14-H14A | 120.3 |
| C14-C15-C16 | 121.9(3) |
| C14-C15-H15A | 119.0 |
| C16-C15-H15A | 119.0 |
| C17-C16-C15 | 118.0(3) |
| C17-C16-H16A | 121.0 |
| C15-C16-H16A | 121.0 |
| C18-C17-C16 | 121.4(3) |
| C18-C17-H17A | 119.3 |
| C16-C17-H17A | 119.3 |
| C17-C18-C13 | 119.6(3) |
| C17-C18-H18A | 120.2 |
| C13-C18-H18A | 120.2 |

Symmetry transformations used to generate equivalent atoms:

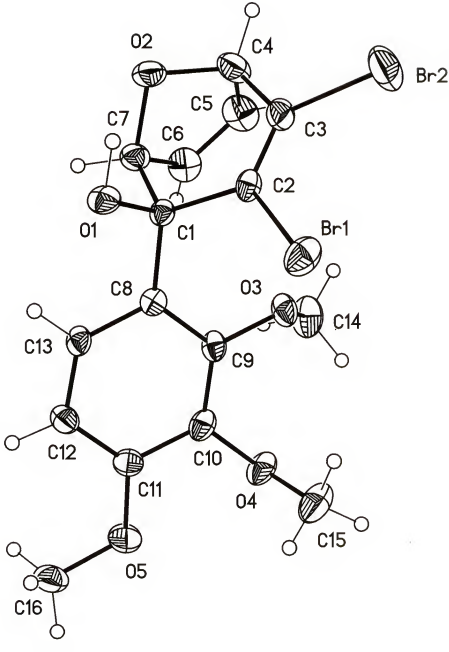
Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **90**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| Br1 | 21(1) | 20(1) | 26(1) | -1(1) | -3(1) | 5(1) |
| Br2 | 30(1) | 27(1) | 25(1) | -7(1) | 3(1) | 3(1) |
| Br3 | 34(1) | 26(1) | 25(1) | 5(1) | 3(1) | -2(1) |
| Br4 | 26(1) | 17(1) | 35(1) | -2(1) | -2(1) | -4(1) |
| O1 | 16(1) | 13(1) | 24(1) | 2(1) | -2(1) | 0(1) |
| N1 | 20(1) | 24(1) | 25(1) | -4(1) | 1(1) | 5(1) |
| N2 | 20(1) | 30(1) | 27(1) | -1(1) | 3(1) | 7(1) |
| N3 | 17(1) | 29(1) | 29(1) | 1(1) | 4(1) | 2(1) |
| C4 | 15(1) | 19(1) | 23(1) | 4(1) | 1(1) | 1(1) |
| C5 | 19(1) | 15(1) | 20(1) | 0(1) | 2(1) | 3(1) |
| C6 | 16(1) | 15(1) | 17(1) | 0(1) | -3(1) | 2(1) |
| C7 | 17(1) | 17(1) | 28(2) | -2(1) | 0(1) | -1(1) |
| C8 | 15(1) | 13(1) | 21(1) | 0(1) | -2(1) | 1(1) |
| C9 | 22(1) | 16(1) | 19(1) | -1(1) | 0(1) | 1(1) |
| C10 | 18(1) | 15(1) | 22(1) | 0(1) | -3(1) | -1(1) |
| C11 | 15(1) | 15(1) | 22(1) | 2(1) | -1(1) | -3(1) |
| C12 | 21(1) | 24(1) | 27(2) | 6(1) | -6(1) | 3(1) |
| C13 | 28(1) | 21(1) | 17(1) | 0(1) | 2(1) | 0(1) |
| C14 | 32(2) | 20(1) | 29(2) | 0(1) | 8(1) | 1(1) |
| C15 | 47(2) | 20(1) | 26(2) | -2(1) | 9(1) | -2(1) |
| C16 | 51(2) | 25(2) | 20(2) | 4(1) | -4(1) | -9(1) |
| C17 | 35(2) | 32(2) | 25(2) | 4(1) | -7(1) | 0(1) |
| C18 | 31(2) | 28(2) | 21(2) | -1(1) | 1(1) | 6(1) |

Table 5. Hydrogen coordinates ( x $10^4$) and isotropic displacement parameters ($Å^2$x $10^3$) for **ro09**.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H4A | 7017 | 750 | 6924 | 23 |
| H5A | 4215 | 352 | 6329 | 22 |
| H7A | 1959 | -1618 | 7713 | 31 |
| H7B | 2758 | -1820 | 6831 | 31 |
| H7C | 1203 | -1034 | 6954 | 31 |
| H12A | 8787 | -858 | 8147 | 36 |
| H12B | 7614 | -634 | 8940 | 36 |
| H12C | 8725 | 194 | 8500 | 36 |
| H14A | 6517 | -2096 | 4912 | 32 |
| H15A | 4801 | -2733 | 3859 | 37 |
| H16A | 1689 | -2370 | 3699 | 38 |
| H17A | 359 | -1259 | 4565 | 37 |
| H18A | 2066 | -558 | 5593 | 32 |

X-Ray data for **106e**



**X-ray experimental for 106e**: Data were collected at 173 K on a Siemens SMART PLATFORM equipped with A CCD area detector and a graphite monochromator utilizing $MoK_\alpha$ radiation ($\lambda = 0.71073$ Å). Cell parameters were refined using up to 8192 reflections. A full sphere of data (1850 frames) was collected using the ω-scan method (0.3° frame width). The first 50 frames were remeasured at the end of data collection to monitor instrument and crystal stability (maximum correction on I was < 1 %). Absorption corrections by integration were applied based on measured indexed crystal faces.

The structure was solved by the Direct Methods in *SHELXTL6,* and refined using full-matrix least squares. The non-H atoms were treated anisotropically, whereas the hydrogen atoms were calculated in ideal positions and were riding on their respective carbon atoms, except the hydroxy proton which was located from a Difference Fourier map and refined riding on its parent oxygen atom. A total of 211 parameters were refined in the final cycle of refinement using 3445 reflections with $I > 2\sigma(I)$ to yield $R_1$ and $wR_2$ of 2.91% and 7.40%, respectively. Refinement was done using $F^2$.

Sheldrick, G. M. (2000). *SHELXTL6*. Bruker-AXS, Madison, Wisconsin, USA.

Table 1. Crystal data and structure refinement for **106e**.

| | | |
|---|---|---|
| Identification code | ro01 | |
| Empirical formula | C16 H16 Br2 O5 | |
| Formula weight | 448.11 | |
| Temperature | 193(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Orthorhombic | |
| Space group | Pna2(1) | |
| Unit cell dimensions | a = 7.2803(4) Å | α= 90°. |
| | b = 26.718(2) Å | β= 90°. |
| | c = 8.5720(5) Å | γ = 90°. |
| Volume | 1667.4(2) $Å^3$ | |
| Z | 4 | |

| | |
|---|---|
| Density (calculated) | 1.785 $Mg/m^3$ |
| Absorption coefficient | 4.883 $mm^{-1}$ |
| F(000) | 888 |
| Crystal size | 0.21 x 0.11 x 0.06 $mm^3$ |
| Theta range for data collection | 2.50 to 27.50°. |
| Index ranges | $-9 \le h \le 9$, $-34 \le k \le 34$, $-11 \le l \le 11$ |
| Reflections collected | 14240 |
| Independent reflections | 3803 [R(int) = 0.0444] |
| Completeness to theta = 27.50° | 99.4 % |
| Absorption correction | Integration |
| Max. and min. transmission | 0.7462 and 0.4166 |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | 3803 / 1 / 211 |
| Goodness-of-fit on $F^2$ | 1.042 |
| Final R indices [I>2sigma(I)] | R1 = 0.0291, wR2 = 0.0740 [3445] |
| R indices (all data) | R1 = 0.0337, wR2 = 0.0760 |
| Absolute structure parameter | 0.010(8) |
| Largest diff. peak and hole | 0.537 and -0.262 e.$Å^{-3}$ |

$R1 = \Sigma(||F_o| - |F_c||) / \Sigma|F_o|$

$wR2 = [\Sigma[w(F_o^2 - F_c^2)^2] / \Sigma[w(F_o^2)^2]]^{1/2}$

$S = [\Sigma[w(F_o^2 - F_c^2)^2] / (n-p)]^{1/2}$

$w = 1/[\sigma^2(F_o^2)+(0.049*p)^2]$, $p = [\max(F_o^2,0)+ 2* F_c^2]/3$

Table 2. Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters ($Å^2$x $10^3$) for **106e**. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| Br1 | 8528(1) | 4538(1) | 7330(1) | 35(1) |
| Br2 | 4461(1) | 4797(1) | 9214(1) | 49(1) |
| O1 | 8772(3) | 3385(1) | 8582(3) | 24(1) |
| O2 | 5016(3) | 3306(1) | 9421(3) | 30(1) |
| O3 | 6087(3) | 3998(1) | 4637(3) | 27(1) |
| O4 | 7882(3) | 3825(1) | 1811(2) | 31(1) |
| O5 | 10363(3) | 3111(1) | 1535(3) | 33(1) |

| | | | | |
|---|---|---|---|---|
| C1 | 7317(4) | 3510(1) | 7532(3) | 18(1) |
| C2 | 6765(4) | 4050(1) | 7864(3) | 21(1) |
| C3 | 5234(5) | 4157(1) | 8630(4) | 27(1) |
| C4 | 3927(4) | 3735(1) | 9029(4) | 32(1) |
| C5 | 2961(4) | 3573(1) | 7563(5) | 37(1) |
| C6 | 4019(4) | 3236(1) | 6882(4) | 30(1) |
| C7 | 5681(4) | 3159(1) | 7906(4) | 25(1) |
| C8 | 8044(4) | 3402(1) | 5899(3) | 18(1) |
| C9 | 7449(4) | 3644(1) | 4530(3) | 21(1) |
| C10 | 8308(4) | 3551(1) | 3124(3) | 25(1) |
| C11 | 9655(4) | 3174(1) | 2990(4) | 24(1) |
| C12 | 10155(4) | 2905(1) | 4320(4) | 24(1) |
| C13 | 9384(4) | 3034(1) | 5730(3) | 21(1) |
| C14 | 4575(5) | 3939(2) | 3564(5) | 38(1) |
| C15 | 8857(6) | 4293(2) | 1757(5) | 41(1) |
| C16 | 11704(5) | 2728(1) | 1331(4) | 32(1) |

Table 3. Bond lengths [Å] and angles [°] for **106e**.

| | |
|---|---|
| Br1-C2 | 1.888(3) |
| Br2-C3 | 1.870(3) |
| O1-C1 | 1.429(3) |
| O1-H1 | 0.9401 |
| O2-C4 | 1.434(4) |
| O2-C7 | 1.441(4) |
| O3-C9 | 1.374(3) |
| O3-C14 | 1.443(4) |
| O4-C10 | 1.379(4) |
| O4-C15 | 1.437(5) |
| O5-C11 | 1.360(4) |
| O5-C16 | 1.424(4) |
| C1-C2 | 1.523(4) |
| C1-C8 | 1.524(4) |
| C1-C7 | 1.550(4) |
| C2-C3 | 1.325(4) |

| | |
|---|---|
| C3-C4 | 1.513(5) |
| C4-C5 | 1.504(5) |
| C4-H4A | 1.0000 |
| C5-C6 | 1.321(5) |
| C5-H5A | 0.9500 |
| C6-C7 | 1.509(5) |
| C6-H6A | 0.9500 |
| C7-H7A | 1.0000 |
| C8-C13 | 1.393(4) |
| C8-C9 | 1.408(4) |
| C9-C10 | 1.381(4) |
| C10-C11 | 1.409(4) |
| C11-C12 | 1.397(4) |
| C12-C13 | 1.376(4) |
| C12-H12A | 0.9500 |
| C13-H13A | 0.9500 |
| C14-H14A | 0.9800 |
| C14-H14B | 0.9800 |
| C14-H14C | 0.9800 |
| C15-H15A | 0.9800 |
| C15-H15B | 0.9800 |
| C15-H15C | 0.9800 |
| C16-H16A | 0.9800 |
| C16-H16B | 0.9800 |
| C16-H16C | 0.9800 |
| C1-O1-H1 | 102.5 |
| C4-O2-C7 | 101.1(2) |
| C9-O3-C14 | 115.7(2) |
| C10-O4-C15 | 112.2(2) |
| C11-O5-C16 | 117.5(3) |
| O1-C1-C2 | 107.4(2) |
| O1-C1-C8 | 106.0(2) |
| C2-C1-C8 | 116.2(2) |
| O1-C1-C7 | 107.3(2) |
| C2-C1-C7 | 109.4(2) |
| C8-C1-C7 | 110.0(2) |

| | |
|---|---|
| C3-C2-C1 | 121.2(3) |
| C3-C2-Br1 | 122.9(2) |
| C1-C2-Br1 | 115.5(2) |
| C2-C3-C4 | 118.7(3) |
| C2-C3-Br2 | 125.7(2) |
| C4-C3-Br2 | 115.5(2) |
| O2-C4-C5 | 103.0(3) |
| O2-C4-C3 | 107.5(2) |
| C5-C4-C3 | 108.6(3) |
| O2-C4-H4A | 112.4 |
| C5-C4-H4A | 112.4 |
| C3-C4-H4A | 112.4 |
| C6-C5-C4 | 107.1(3) |
| C6-C5-H5A | 126.5 |
| C4-C5-H5A | 126.5 |
| C5-C6-C7 | 107.7(3) |
| C5-C6-H6A | 126.2 |
| C7-C6-H6A | 126.2 |
| O2-C7-C6 | 102.6(2) |
| O2-C7-C1 | 106.2(2) |
| C6-C7-C1 | 114.4(3) |
| O2-C7-H7A | 111.1 |
| C6-C7-H7A | 111.1 |
| C1-C7-H7A | 111.1 |
| C13-C8-C9 | 116.9(3) |
| C13-C8-C1 | 118.2(2) |
| C9-C8-C1 | 124.9(3) |
| O3-C9-C10 | 120.6(2) |
| O3-C9-C8 | 118.9(2) |
| C10-C9-C8 | 120.4(3) |
| O4-C10-C9 | 121.0(3) |
| O4-C10-C11 | 118.0(3) |
| C9-C10-C11 | 121.0(3) |
| O5-C11-C12 | 125.9(3) |
| O5-C11-C10 | 115.3(3) |
| C12-C11-C10 | 118.9(3) |

| | |
|---|---|
| C13-C12-C11 | 118.8(3) |
| C13-C12-H12A | 120.6 |
| C11-C12-H12A | 120.6 |
| C12-C13-C8 | 123.6(3) |
| C12-C13-H13A | 118.2 |
| C8-C13-H13A | 118.2 |
| O3-C14-H14A | 109.5 |
| O3-C14-H14B | 109.5 |
| H14A-C14-H14B | 109.5 |
| O3-C14-H14C | 109.5 |
| H14A-C14-H14C | 109.5 |
| H14B-C14-H14C | 109.5 |
| O4-C15-H15A | 109.5 |
| O4-C15-H15B | 109.5 |
| H15A-C15-H15B | 109.5 |
| O4-C15-H15C | 109.5 |
| H15A-C15-H15C | 109.5 |
| H15B-C15-H15C | 109.5 |
| O5-C16-H16A | 109.5 |
| O5-C16-H16B | 109.5 |
| H16A-C16-H16B | 109.5 |
| O5-C16-H16C | 109.5 |
| H16A-C16-H16C | 109.5 |
| H16B-C16-H16C | 109.5 |

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **106e**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| Br1 | 43(1) | 27(1) | 35(1) | 3(1) | -1(1) | -11(1) |
| Br2 | 59(1) | 32(1) | 56(1) | -11(1) | 4(1) | 14(1) |
| O1 | 24(1) | 33(1) | 15(1) | 0(1) | -3(1) | 2(1) |
| O2 | 34(1) | 30(1) | 27(1) | 2(1) | 12(1) | -3(1) |

| | | | | | | |
|---|---|---|---|---|---|---|
| O3 | 27(1) | 28(1) | 25(1) | -1(1) | -7(1) | 9(1) |
| O4 | 44(1) | 30(1) | 18(1) | 6(1) | -7(1) | 0(1) |
| O5 | 44(2) | 37(1) | 20(1) | -3(1) | 6(1) | 8(1) |
| C1 | 21(1) | 17(1) | 17(1) | 0(1) | -2(1) | 0(1) |
| C2 | 25(1) | 14(1) | 23(1) | 0(1) | -5(1) | -3(1) |
| C3 | 36(2) | 21(1) | 25(1) | -3(1) | 0(1) | 2(1) |
| C4 | 28(2) | 32(2) | 37(2) | -6(2) | 10(1) | 2(1) |
| C5 | 19(1) | 40(2) | 51(2) | -2(2) | 3(1) | -5(1) |
| C6 | 23(1) | 30(2) | 37(2) | -2(1) | -4(1) | -8(1) |
| C7 | 28(2) | 22(2) | 24(1) | -2(1) | 5(1) | -2(1) |
| C8 | 18(1) | 19(1) | 18(1) | -1(1) | -4(1) | -2(1) |
| C9 | 22(1) | 21(1) | 21(1) | 0(1) | -8(1) | 4(1) |
| C10 | 31(2) | 23(2) | 20(2) | 4(1) | -6(1) | -1(1) |
| C11 | 28(2) | 26(2) | 19(1) | -3(1) | 1(1) | 1(1) |
| C12 | 24(1) | 25(1) | 23(1) | -3(1) | 1(1) | 3(1) |
| C13 | 23(1) | 23(1) | 18(1) | 2(1) | -5(1) | 5(1) |
| C14 | 33(2) | 40(2) | 42(2) | 4(2) | -18(2) | 7(1) |
| C15 | 60(2) | 32(2) | 32(2) | 9(2) | -4(2) | -4(2) |
| C16 | 34(2) | 33(2) | 30(2) | -5(1) | 10(1) | 0(1) |

Table 5. Hydrogen coordinates ( x $10^4$) and isotropic displacement parameters ($Å^2$x $10^3$) for **106e**.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H1 | 8263 | 3463 | 9559 | 36 |
| H4A | 3050 | 3828 | 9878 | 38 |
| H5A | 1809 | 3691 | 7196 | 44 |
| H6A | 3776 | 3071 | 5921 | 36 |
| H7A | 6074 | 2800 | 7903 | 30 |
| H12A | 11012 | 2638 | 4253 | 29 |
| H13A | 9787 | 2862 | 6638 | 26 |
| H14A | 4795 | 4144 | 2634 | 58 |
| H14B | 3434 | 4047 | 4069 | 58 |

| | | | | |
|---|---|---|---|---|
| H14C | 4469 | 3587 | 3261 | 58 |
| H15A | 8728 | 4465 | 2760 | 62 |
| H15B | 8347 | 4502 | 925 | 62 |
| H15C | 10160 | 4229 | 1549 | 62 |
| H16A | 12740 | 2789 | 2036 | 48 |
| H16B | 12140 | 2731 | 250 | 48 |
| H16C | 11155 | 2402 | 1568 | 48 |

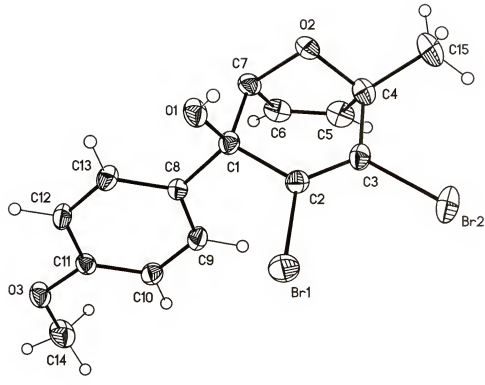
Table 6. Hydrogen bonds for **106e** [Å and °].

| D-H...A | d(D-H) | d(H...A) | d(D...A) | <(DHA) |
|---|---|---|---|---|
| O1-H1...O4#1 | 0.94(2) | 2.18(2) | 3.077(3) | 160.0(2) |

Symmetry transformations used to generate equivalent atoms:

#1 x,y,z+1

X-Ray data for **114**




**X-ray experimental for 114**: Data were collected at 173 K on a Siemens SMART PLATFORM equipped with A CCD area detector and a graphite monochromator utilizing $MoK_\alpha$ radiation ($\lambda = 0.71073$ Å). Cell parameters were refined using up to 8192 reflections. A full sphere of data (1850 frames) was collected using the ω-scan method (0.3° frame width). The first 50 frames were remeasured at the end of data collection to monitor instrument and crystal stability (maximum correction on I was < 1 %). Absorption corrections by integration were applied based on measured indexed crystal faces.

The structure was solved by the Direct Methods in *SHELXTL5,* and refined using full-matrix least squares. The non-H atoms were treated anisotropically, whereas the hydrogen atoms were calculated in ideal positions and were riding on their respective

carbon atoms. The asymmetric unit consists or two chemically equivalent but crystallographically independent molecules. They differ mainly in the orientation of the methoxy methyl group. The hydroxyl H1 and H1' atoms were located from a difference Fourier map but did not refine properly. Thus they were constrained to ideal positions and refined riding on their respective Oxygen atoms. A total of 367 parameters were refined in the final cycle of refinement using 6609 reflections with $I > 2\sigma(I)$ to yield $R_1$ and $wR_2$ of 3.19% and 8.27%, respectively. Refinement was done using $F^2$.

Sheldrick, G. M. (2000). *SHELXTL5*. Bruker-AXS, Madison, Wisconsin, USA.

Table 1. Crystal data and structure refinement for **114**.

| | | |
|---|---|---|
| Identification code | ro05 | |
| Empirical formula | C15 H13 Br2 O3 | |
| Formula weight | 401.07 | |
| Temperature | 193(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Orthorhombic | |
| Space group | Pbca | |
| Unit cell dimensions | a = 18.3151(7) Å | α= 90°. |
| | b = 16.3060(7) Å | β= 90°. |
| | c = 19.7968(8) Å | γ = 90°. |
| Volume | 5912.2(4) $Å^3$ | |
| Z | 16 | |
| Density (calculated) | 1.802 $Mg/m^3$ | |
| Absorption coefficient | 5.488 $mm^{-1}$ | |
| F(000) | 3152 | |
| Crystal size | 0.34 x 0.18 x 0.10 $mm^3$ | |
| Theta range for data collection | 1.96 to 27.50°. | |
| Index ranges | $-23 \le h \le 23$, $-21 \le k \le 21$, $-24 \le l \le 24$ | |
| Reflections collected | 48666 | |
| Independent reflections | 6609 [R(int) = 0.0365] | |
| Completeness to theta = 27.50° | 97.4 % | |
| Absorption correction | Integration | |

| | |
|---|---|
| Max. and min. transmission | 0.5825 and 0.2723 |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | 6609 / 0 / 367 |
| Goodness-of-fit on $F^2$ | 1.027 |
| Final R indices [I>2sigma(I)] | R1 = 0.0319, wR2 = 0.0827 [5404] |
| R indices (all data) | R1 = 0.0442, wR2 = 0.0888 |
| Largest diff. peak and hole | 0.923 and -0.648 e.$Å^{-3}$ |

$R1 = \Sigma(||F_o| - |F_c||) / \Sigma|F_o|$

$wR2 = [\Sigma[w(F_o^2 - F_c^2)^2] / \Sigma[w(F_o^2)^2]]^{1/2}$

$S = [\Sigma[w(F_o^2 - F_c^2)^2] / (n-p)]^{1/2}$

$w = 1/[\sigma^2(F_o^2)+(0.044*p)^2+8.92*p]$, $p = [\max(F_o^2,0)+ 2* F_c^2]/3$

Table 2. Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters ($Å^2$x $10^3$) for **114**. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| Br1 | 5655(1) | 4565(1) | 1258(1) | 42(1) |
| Br2 | 4584(1) | 3679(1) | 2445(1) | 49(1) |
| O1 | 4576(1) | 6067(1) | 849(1) | 30(1) |
| O2 | 3664(1) | 5893(1) | 2047(1) | 29(1) |
| O3 | 7437(1) | 7951(1) | 1516(1) | 33(1) |
| C1 | 4843(2) | 6041(2) | 1522(1) | 24(1) |
| C2 | 4926(2) | 5139(2) | 1732(2) | 25(1) |
| C3 | 4488(2) | 4787(2) | 2179(2) | 28(1) |
| C4 | 3901(2) | 5298(2) | 2538(2) | 31(1) |
| C5 | 4301(2) | 5835(2) | 3046(2) | 35(1) |
| C6 | 4520(2) | 6496(2) | 2731(2) | 33(1) |
| C7 | 4274(2) | 6449(2) | 2001(2) | 27(1) |
| C8 | 5556(2) | 6518(2) | 1539(2) | 23(1) |
| C9 | 6082(2) | 6400(2) | 2037(2) | 30(1) |
| C10 | 6716(2) | 6869(2) | 2049(2) | 29(1) |
| C11 | 6835(2) | 7457(2) | 1555(1) | 25(1) |
| C12 | 6313(2) | 7578(2) | 1055(2) | 29(1) |
| C13 | 5681(2) | 7119(2) | 1052(2) | 27(1) |

| | | | | |
|---|---|---|---|---|
| C14 | 7950(2) | 7908(2) | 2058(2) | 44(1) |
| C15 | 3234(2) | 4832(3) | 2783(2) | 48(1) |
| Br1' | 1210(1) | 4479(1) | 1632(1) | 35(1) |
| Br2' | 2404(1) | 3097(1) | 1012(1) | 39(1) |
| O1' | 2268(1) | 6124(1) | 1451(1) | 30(1) |
| O2' | 3249(1) | 5334(1) | 561(1) | 28(1) |
| O3' | -729(1) | 6893(2) | 29(1) | 40(1) |
| C1' | 2032(2) | 5684(2) | 866(2) | 23(1) |
| C2' | 1980(2) | 4768(2) | 1042(1) | 24(1) |
| C3' | 2465(2) | 4222(2) | 816(1) | 25(1) |
| C4' | 3088(2) | 4504(2) | 350(2) | 26(1) |
| C5' | 2766(2) | 4644(2) | -348(2) | 30(1) |
| C6' | 2490(2) | 5394(2) | -362(2) | 31(1) |
| C7' | 2628(2) | 5797(2) | 319(2) | 28(1) |
| C8' | 1305(2) | 6038(2) | 648(1) | 23(1) |
| C9' | 1019(2) | 6736(2) | 946(2) | 26(1) |
| C10' | 345(2) | 7053(2) | 748(2) | 28(1) |
| C11' | -48(2) | 6663(2) | 249(2) | 29(1) |
| C12' | 242(2) | 5979(2) | -72(2) | 31(1) |
| C13' | 903(2) | 5662(2) | 131(2) | 28(1) |
| C14' | -1069(2) | 7547(3) | 384(2) | 50(1) |
| C15' | 3785(2) | 4008(2) | 396(2) | 34(1) |

Table 3. Bond lengths [Å] and angles [°] for **114**.

| | |
|---|---|
| Br1-C2 | 1.881(3) |
| Br2-C3 | 1.891(3) |
| O1-C1 | 1.419(3) |
| O1-H1 | 0.8400 |
| O2-C4 | 1.441(4) |
| O2-C7 | 1.442(3) |
| O3-C11 | 1.367(3) |
| O3-C14 | 1.428(4) |
| C1-C8 | 1.520(4) |
| C1-C2 | 1.536(4) |

| | |
|---|---|
| C1-C7 | 1.558(4) |
| C2-C3 | 1.325(4) |
| C3-C4 | 1.535(4) |
| C4-C15 | 1.516(4) |
| C4-C5 | 1.522(4) |
| C5-C6 | 1.308(5) |
| C5-H5A | 0.9500 |
| C6-C7 | 1.516(4) |
| C6-H6A | 0.9500 |
| C8-C9 | 1.392(4) |
| C8-C13 | 1.394(4) |
| C9-C10 | 1.390(4) |
| C9-H9A | 0.9500 |
| C10-C11 | 1.387(4) |
| C10-H10A | 0.9500 |
| C11-C12 | 1.391(4) |
| C12-C13 | 1.379(4) |
| C12-H12A | 0.9500 |
| C13-H13A | 0.9500 |
| C14-H14A | 0.9800 |
| C14-H14B | 0.9800 |
| C14-H14C | 0.9800 |
| C15-H15A | 0.9800 |
| C15-H15B | 0.9800 |
| C15-H15C | 0.9800 |
| Br1'-C2' | 1.890(3) |
| Br2'-C3' | 1.879(3) |
| O1'-C1' | 1.428(3) |
| O1'-H1' | 0.8400 |
| O2'-C4' | 1.446(3) |
| O2'-C7' | 1.447(4) |
| O3'-C11' | 1.374(4) |
| O3'-C14' | 1.420(4) |
| C1'-C8' | 1.515(4) |
| C1'-C2' | 1.537(4) |
| C1'-C7' | 1.548(4) |

| | |
|---|---|
| C2'-C3' | 1.336(4) |
| C3'-C4' | 1.538(4) |
| C4'-C15' | 1.514(4) |
| C4'-C5' | 1.521(4) |
| C5'-C6' | 1.324(5) |
| C5'-H5'A | 0.9500 |
| C6'-C7' | 1.520(4) |
| C6'-H6'A | 0.9500 |
| C8'-C9' | 1.385(4) |
| C8'-C13' | 1.402(4) |
| C9'-C10' | 1.394(4) |
| C9'-H9'A | 0.9500 |
| C10'-C11' | 1.379(4) |
| C10'-H10B | 0.9500 |
| C11'-C12' | 1.389(4) |
| C12'-C13' | 1.376(4) |
| C12'-H12B | 0.9500 |
| C13'-H13B | 0.9500 |
| C14'-H14D | 0.9800 |
| C14'-H14E | 0.9800 |
| C14'-H14F | 0.9800 |
| C15'-H15D | 0.9800 |
| C15'-H15E | 0.9800 |
| C15'-H15F | 0.9800 |
| C1-O1-H1 | 109.5 |
| C4-O2-C7 | 103.4(2) |
| C11-O3-C14 | 117.3(2) |
| O1-C1-C8 | 107.6(2) |
| O1-C1-C2 | 108.6(2) |
| C8-C1-C2 | 113.5(2) |
| O1-C1-C7 | 109.1(2) |
| C8-C1-C7 | 109.9(2) |
| C2-C1-C7 | 108.0(2) |
| C3-C2-C1 | 122.4(3) |
| C3-C2-Br1 | 123.2(2) |
| C1-C2-Br1 | 114.3(2) |

| | |
|---|---|
| C2-C3-C4 | 119.9(3) |
| C2-C3-Br2 | 122.9(2) |
| C4-C3-Br2 | 117.0(2) |
| O2-C4-C15 | 108.1(3) |
| O2-C4-C5 | 101.7(3) |
| C15-C4-C5 | 117.7(3) |
| O2-C4-C3 | 105.3(2) |
| C15-C4-C3 | 116.2(3) |
| C5-C4-C3 | 106.3(3) |
| C6-C5-C4 | 107.9(3) |
| C6-C5-H5A | 126.0 |
| C4-C5-H5A | 126.0 |
| C5-C6-C7 | 108.8(3) |
| C5-C6-H6A | 125.6 |
| C7-C6-H6A | 125.6 |
| O2-C7-C6 | 101.7(2) |
| O2-C7-C1 | 106.7(2) |
| C6-C7-C1 | 113.9(2) |
| C9-C8-C13 | 118.3(3) |
| C9-C8-C1 | 122.7(3) |
| C13-C8-C1 | 119.0(3) |
| C10-C9-C8 | 120.9(3) |
| C10-C9-H9A | 119.6 |
| C8-C9-H9A | 119.6 |
| C11-C10-C9 | 120.1(3) |
| C11-C10-H10A | 120.0 |
| C9-C10-H10A | 120.0 |
| O3-C11-C10 | 125.1(3) |
| O3-C11-C12 | 115.5(2) |
| C10-C11-C12 | 119.4(3) |
| C13-C12-C11 | 120.3(3) |
| C13-C12-H12A | 119.8 |
| C11-C12-H12A | 119.8 |
| C12-C13-C8 | 121.0(3) |
| C12-C13-H13A | 119.5 |
| C8-C13-H13A | 119.5 |

| | |
|---|---|
| O3-C14-H14A | 109.5 |
| O3-C14-H14B | 109.5 |
| H14A-C14-H14B | 109.5 |
| O3-C14-H14C | 109.5 |
| H14A-C14-H14C | 109.5 |
| H14B-C14-H14C | 109.5 |
| C4-C15-H15A | 109.5 |
| C4-C15-H15B | 109.5 |
| H15A-C15-H15B | 109.5 |
| C4-C15-H15C | 109.5 |
| H15A-C15-H15C | 109.5 |
| H15B-C15-H15C | 109.5 |
| C1'-O1'-H1' | 109.5 |
| C4'-O2'-C7' | 103.5(2) |
| C11'-O3'-C14' | 116.6(3) |
| O1'-C1'-C8' | 107.8(2) |
| O1'-C1'-C2' | 108.8(2) |
| C8'-C1'-C2' | 112.3(2) |
| O1'-C1'-C7' | 107.1(2) |
| C8'-C1'-C7' | 112.1(2) |
| C2'-C1'-C7' | 108.6(2) |
| C3'-C2'-C1' | 122.0(3) |
| C3'-C2'-Br1' | 122.5(2) |
| C1'-C2'-Br1' | 115.46(19) |
| C2'-C3'-C4' | 119.7(3) |
| C2'-C3'-Br2' | 122.9(2) |
| C4'-C3'-Br2' | 117.4(2) |
| O2'-C4'-C15' | 108.1(2) |
| O2'-C4'-C5' | 101.6(2) |
| C15'-C4'-C5' | 117.5(3) |
| O2'-C4'-C3' | 105.0(2) |
| C15'-C4'-C3' | 115.5(3) |
| C5'-C4'-C3' | 107.6(2) |
| C6'-C5'-C4' | 107.8(3) |
| C6'-C5'-H5'A | 126.1 |
| C4'-C5'-H5'A | 126.1 |

| | |
|---|---|
| C5'-C6'-C7' | 108.5(3) |
| C5'-C6'-H6'A | 125.7 |
| C7'-C6'-H6'A | 125.7 |
| O2'-C7'-C6' | 101.5(2) |
| O2'-C7'-C1' | 105.1(2) |
| C6'-C7'-C1' | 116.8(2) |
| C9'-C8'-C13' | 118.2(3) |
| C9'-C8'-C1' | 121.6(3) |
| C13'-C8'-C1' | 120.2(3) |
| C8'-C9'-C10' | 121.3(3) |
| C8'-C9'-H9'A | 119.4 |
| C10'-C9'-H9'A | 119.4 |
| C11'-C10'-C9' | 119.5(3) |
| C11'-C10'-H10B | 120.2 |
| C9'-C10'-H10B | 120.2 |
| O3'-C11'-C10' | 125.1(3) |
| O3'-C11'-C12' | 114.9(3) |
| C10'-C11'-C12' | 120.0(3) |
| C13'-C12'-C11' | 120.2(3) |
| C13'-C12'-H12B | 119.9 |
| C11'-C12'-H12B | 119.9 |
| C12'-C13'-C8' | 120.8(3) |
| C12'-C13'-H13B | 119.6 |
| C8'-C13'-H13B | 119.6 |
| O3'-C14'-H14D | 109.5 |
| O3'-C14'-H14E | 109.5 |
| H14D-C14'-H14E | 109.5 |
| O3'-C14'-H14F | 109.5 |
| H14D-C14'-H14F | 109.5 |
| H14E-C14'-H14F | 109.5 |
| C4'-C15'-H15D | 109.5 |
| C4'-C15'-H15E | 109.5 |
| H15D-C15'-H15E | 109.5 |
| C4'-C15'-H15F | 109.5 |
| H15D-C15'-H15F | 109.5 |
| H15E-C15'-H15F | 109.5 |

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **114**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| Br1 | 40(1) | 35(1) | 50(1) | -3(1) | 10(1) | 8(1) |
| Br2 | 63(1) | 28(1) | 54(1) | 12(1) | 0(1) | -7(1) |
| O1 | 29(1) | 34(1) | 28(1) | 6(1) | -6(1) | -10(1) |
| O2 | 22(1) | 33(1) | 32(1) | -1(1) | 0(1) | -4(1) |
| O3 | 30(1) | 35(1) | 35(1) | 5(1) | -3(1) | -10(1) |
| C1 | 25(1) | 23(1) | 23(1) | 3(1) | -3(1) | -2(1) |
| C2 | 25(1) | 22(1) | 29(1) | -2(1) | -2(1) | 0(1) |
| C3 | 32(2) | 22(1) | 29(2) | 2(1) | -2(1) | -5(1) |
| C4 | 31(2) | 35(2) | 27(2) | 0(1) | 3(1) | -7(1) |
| C5 | 37(2) | 42(2) | 25(2) | -8(1) | -1(1) | 0(1) |
| C6 | 29(2) | 35(2) | 34(2) | -11(1) | -1(1) | 1(1) |
| C7 | 22(1) | 25(1) | 35(2) | -2(1) | 0(1) | -3(1) |
| C8 | 23(1) | 21(1) | 26(1) | 2(1) | 1(1) | 0(1) |
| C9 | 30(2) | 30(2) | 29(2) | 10(1) | -2(1) | -1(1) |
| C10 | 26(1) | 32(2) | 29(2) | 6(1) | -5(1) | 0(1) |
| C11 | 23(1) | 23(1) | 28(1) | -1(1) | 2(1) | -3(1) |
| C12 | 34(2) | 25(1) | 29(2) | 9(1) | -1(1) | -5(1) |
| C13 | 32(2) | 25(1) | 24(1) | 4(1) | -6(1) | -2(1) |
| C14 | 32(2) | 53(2) | 47(2) | 4(2) | -6(2) | -15(2) |
| C15 | 41(2) | 57(2) | 46(2) | 4(2) | 14(2) | -16(2) |
| Br1' | 35(1) | 35(1) | 35(1) | 7(1) | 10(1) | 3(1) |
| Br2' | 48(1) | 26(1) | 45(1) | 1(1) | 4(1) | 3(1) |
| O1' | 25(1) | 31(1) | 34(1) | -13(1) | -7(1) | 5(1) |
| O2' | 21(1) | 26(1) | 37(1) | -6(1) | 0(1) | -1(1) |
| O3' | 30(1) | 41(1) | 50(1) | 0(1) | -8(1) | 8(1) |
| C1' | 23(1) | 22(1) | 26(1) | -4(1) | -1(1) | -2(1) |
| C2' | 24(1) | 25(1) | 22(1) | 0(1) | 2(1) | 0(1) |
| C3' | 30(2) | 21(1) | 24(1) | 0(1) | -3(1) | 0(1) |
| C4' | 25(1) | 27(1) | 27(2) | -5(1) | 2(1) | 1(1) |

| | | | | | | |
|---|---|---|---|---|---|---|
| C5' | 30(2) | 37(2) | 24(2) | -2(1) | 4(1) | 0(1) |
| C6' | 30(2) | 37(2) | 25(2) | 3(1) | 5(1) | 0(1) |
| C7' | 23(1) | 27(1) | 33(2) | 0(1) | 3(1) | -1(1) |
| C8' | 21(1) | 21(1) | 28(1) | 2(1) | 1(1) | -4(1) |
| C9' | 26(1) | 23(1) | 30(2) | 0(1) | 1(1) | -3(1) |
| C10' | 29(2) | 23(1) | 33(2) | 4(1) | 7(1) | 2(1) |
| C11' | 24(1) | 30(2) | 34(2) | 11(1) | 0(1) | -1(1) |
| C12' | 30(2) | 29(2) | 34(2) | 2(1) | -8(1) | -5(1) |
| C13' | 26(2) | 25(1) | 34(2) | 1(1) | -1(1) | -2(1) |
| C14' | 42(2) | 55(2) | 52(2) | -2(2) | -6(2) | 22(2) |
| C15' | 29(2) | 36(2) | 37(2) | -4(1) | 1(1) | 8(1) |

Table 5. Hydrogen coordinates ( x $10^4$) and isotropic displacement parameters ($Å^2$x $10^3$) for **114**.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H1 | 4183 | 5803 | 825 | 45 |
| H5A | 4377 | 5713 | 3510 | 42 |
| H6A | 4788 | 6934 | 2928 | 39 |
| H9A | 6007 | 5993 | 2373 | 36 |
| H10A | 7067 | 6787 | 2395 | 35 |
| H12A | 6391 | 7980 | 715 | 35 |
| H13A | 5325 | 7213 | 711 | 33 |
| H14A | 7700 | 8019 | 2486 | 66 |
| H14B | 8335 | 8317 | 1988 | 66 |
| H14C | 8167 | 7359 | 2072 | 66 |
| H15A | 2882 | 5219 | 2976 | 72 |
| H15B | 3381 | 4435 | 3129 | 72 |
| H15C | 3010 | 4542 | 2402 | 72 |
| H1' | 2676 | 5943 | 1576 | 45 |
| H5'A | 2763 | 4261 | -710 | 37 |
| H6'A | 2246 | 5639 | -734 | 37 |
| H9'A | 1287 | 7004 | 1293 | 31 |

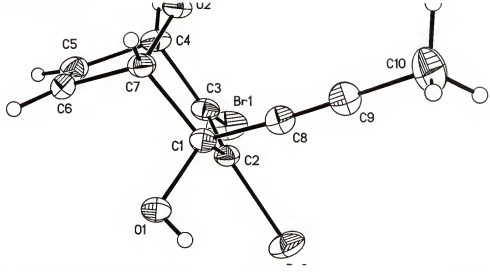
| | | | | |
|---|---|---|---|---|
| H10B | 159 | 7535 | 956 | 34 |
| H12B | -17 | 5729 | -434 | 37 |
| H13B | 1088 | 5183 | -81 | 34 |
| H14D | -1047 | 7440 | 870 | 75 |
| H14E | -1581 | 7591 | 243 | 75 |
| H14F | -815 | 8062 | 283 | 75 |
| H15D | 4170 | 4280 | 135 | 52 |
| H15E | 3700 | 3458 | 213 | 52 |
| H15F | 3936 | 3965 | 870 | 52 |

Table 6. Hydrogen bonds for **114** [Å and °].

| D-H...A | d(D-H) | d(H...A) | d(D...A) | <(DHA) |
|---|---|---|---|---|
| O1-H1...O2' | 0.84 | 1.95 | 2.768(3) | 166.0 |
| O1'-H1'...O2 | 0.84 | 2.04 | 2.840(3) | 159.9 |

Symmetry transformations used to generate equivalent atoms:

X-Ray data for **115e**




**X-ray experimental for 115e**: Data were collected at 173 K on a Siemens SMART PLATFORM equipped with A CCD area detector and a graphite monochromator utilizing $MoK_\alpha$ radiation ($\lambda = 0.71073$ Å). Cell parameters were refined using up to 8192 reflections. A full sphere of data (1850 frames) was collected using the ω-scan method (0.3° frame width). The first 50 frames were remeasured at the end of data collection to monitor instrument and crystal stability (maximum correction on I was < 1 %). Absorption corrections by integration were applied based on measured indexed crystal faces.

The structure was solved by the Direct Methods in *SHELXTL5,* and refined using full-matrix least squares. The non-H atoms were treated anisotropically, whereas the hydrogen atoms were calculated in ideal positions and were riding on their respective carbon atoms. A total of 133 parameters were refined in the final cycle of refinement using 2228 reflections with $I > 2\sigma(I)$ to yield $R_1$ and $wR_2$ of 2.53% and 7.03%, respectively. Refinement was done using $F^2$.

Sheldrick, G. M. (2000). *SHELXTL5*. Bruker-AXS, Madison, Wisconsin, USA.

Table 1. Crystal data and structure refinement for **115e**.

| | | |
|---|---|---|
| Identification code | ro07 | |
| Empirical formula | C10 H8 Br2 O2 | |
| Formula weight | 319.98 | |
| Temperature | 193(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Monoclinic | |
| Space group | P2(1)/c | |
| Unit cell dimensions | a = 11.7974(6) Å | α= 90°. |
| | b = 8.1389(4) Å | β= 98.719(2)°. |
| | c = 11.4455(5) Å | γ = 90°. |
| Volume | 1086.27(9) $Å^3$ | |
| Z | 4 | |
| Density (calculated) | 1.957 $Mg/m^3$ | |
| Absorption coefficient | 7.433 $mm^{-1}$ | |
| F(000) | 616 | |
| Crystal size | 0.21 x 0.19 x 0.12 $mm^3$ | |
| Theta range for data collection | 1.75 to 27.50°. | |
| Index ranges | $-15 \le h \le 15$, $-10 \le k \le 10$, $-14 \le l \le 14$ | |
| Reflections collected | 9390 | |
| Independent reflections | 2492 [R(int) = 0.0651] | |
| Completeness to theta = 27.50° | 99.8 % | |
| Absorption correction | Integration | |
| Max. and min. transmission | 0.4712 and 0.2179 | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 2492 / 0 / 133 | |
| Goodness-of-fit on $F^2$ | 1.065 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0253, wR2 = 0.0703 [2228] | |
| R indices (all data) | R1 = 0.0290, wR2 = 0.0714 | |
| Extinction coefficient | 0.0044(5) | |
| Largest diff. peak and hole | 0.755 and -0.643 e.$Å^{-3}$ | |

$R1 = \sum(||F_o| - |F_c||) / \sum|F_o|$

$wR2 = [\sum[w(F_o^2 - F_c^2)^2] / \sum[w(F_o^2)^2]]^{1/2}$

$S = [\sum[w(F_o^2 - F_c^2)^2] / (n-p)]^{1/2}$

$w = 1/[\sigma^2(F_o^2)+(0.0370*p)^2+0.31*p]$, $p = [\max(F_o^2,0)+ 2* F_c^2]/3$

Table 2. Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters ($Å^2$x $10^3$) for **115e**. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| Br1 | 2585(1) | 8167(1) | 4211(1) | 38(1) |
| Br2 | 1837(1) | 5080(1) | 5980(1) | 32(1) |
| O1 | 3456(2) | 2150(2) | 5299(2) | 21(1) |
| C9 | 739(2) | 1373(3) | 3738(2) | 26(1) |
| C8 | 1626(2) | 2059(3) | 4039(2) | 21(1) |
| C4 | 3354(2) | 5498(3) | 2861(2) | 22(1) |
| C1 | 2735(2) | 2907(3) | 4349(2) | 17(1) |
| C2 | 2513(2) | 4726(3) | 4615(2) | 18(1) |
| O2 | 2877(1) | 3954(2) | 2414(1) | 21(1) |
| C7 | 3414(2) | 2807(3) | 3286(2) | 19(1) |
| C6 | 4614(2) | 3484(3) | 3591(2) | 24(1) |
| C3 | 2787(2) | 5926(3) | 3927(2) | 20(1) |
| C5 | 4596(2) | 5055(3) | 3320(2) | 26(1) |
| C10 | -340(2) | 508(4) | 3360(3) | 42(1) |

Table 3. Bond lengths [Å] and angles [°] for **115e**.

| | |
|---|---|
| Br1-C3 | 1.875(2) |
| Br2-C2 | 1.881(2) |
| O1-C1 | 1.416(3) |
| O1-H1 | 0.69(3) |
| C9-C8 | 1.190(3) |
| C9-C10 | 1.462(3) |
| C8-C1 | 1.474(3) |
| C4-O2 | 1.440(3) |
| C4-C3 | 1.518(3) |
| C4-C5 | 1.523(3) |
| C4-H4A | 1.0000 |
| C1-C2 | 1.542(3) |
| C1-C7 | 1.557(3) |

| | |
|---|---|
| C2-C3 | 1.325(3) |
| O2-C7 | 1.441(3) |
| C7-C6 | 1.511(3) |
| C7-H7A | 1.0000 |
| C6-C5 | 1.315(4) |
| C6-H6A | 0.9500 |
| C5-H5A | 0.9500 |
| C10-H10A | 0.9800 |
| C10-H10B | 0.9800 |
| C10-H10C | 0.9800 |

| | |
|---|---|
| C1-O1-H1 | 108(3) |
| C8-C9-C10 | 179.1(3) |
| C9-C8-C1 | 177.0(3) |
| O2-C4-C3 | 106.78(18) |
| O2-C4-C5 | 102.72(18) |
| C3-C4-C5 | 107.18(19) |
| O2-C4-H4A | 113.1 |
| C3-C4-H4A | 113.1 |
| C5-C4-H4A | 113.1 |
| O1-C1-C8 | 112.89(18) |
| O1-C1-C2 | 111.48(18) |
| C8-C1-C2 | 109.02(18) |
| O1-C1-C7 | 104.92(17) |
| C8-C1-C7 | 109.32(18) |
| C2-C1-C7 | 109.08(18) |
| C3-C2-C1 | 121.8(2) |
| C3-C2-Br2 | 123.55(17) |
| C1-C2-Br2 | 114.64(15) |
| C4-O2-C7 | 102.26(16) |
| O2-C7-C6 | 102.85(18) |
| O2-C7-C1 | 106.45(17) |
| C6-C7-C1 | 112.07(18) |
| O2-C7-H7A | 111.7 |
| C6-C7-H7A | 111.7 |
| C1-C7-H7A | 111.7 |

| | |
|---|---|
| C5-C6-C7 | 108.6(2) |
| C5-C6-H6A | 125.7 |
| C7-C6-H6A | 125.7 |
| C2-C3-C4 | 119.0(2) |
| C2-C3-Br1 | 124.43(18) |
| C4-C3-Br1 | 116.47(16) |
| C6-C5-C4 | 107.0(2) |
| C6-C5-H5A | 126.5 |
| C4-C5-H5A | 126.5 |
| C9-C10-H10A | 109.5 |
| C9-C10-H10B | 109.5 |
| H10A-C10-H10B | 109.5 |
| C9-C10-H10C | 109.5 |
| H10A-C10-H10C | 109.5 |
| H10B-C10-H10C | 109.5 |

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **115e**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| Br1 | 65(1) | 17(1) | 31(1) | 1(1) | 9(1) | 5(1) |
| Br2 | 44(1) | 32(1) | 23(1) | -1(1) | 14(1) | 8(1) |
| O1 | 23(1) | 24(1) | 17(1) | 6(1) | 3(1) | 1(1) |
| C9 | 25(1) | 25(1) | 27(1) | 1(1) | 3(1) | 0(1) |
| C8 | 23(1) | 19(1) | 21(1) | 1(1) | 4(1) | 1(1) |
| C4 | 30(1) | 21(1) | 15(1) | 0(1) | 5(1) | -5(1) |
| C1 | 19(1) | 16(1) | 16(1) | 1(1) | 2(1) | 0(1) |
| C2 | 20(1) | 20(1) | 13(1) | -2(1) | 2(1) | 1(1) |
| O2 | 24(1) | 24(1) | 13(1) | -1(1) | 1(1) | -2(1) |
| C7 | 22(1) | 20(1) | 15(1) | -1(1) | 3(1) | 2(1) |
| C6 | 18(1) | 36(1) | 18(1) | -3(1) | 4(1) | 1(1) |
| C3 | 27(1) | 16(1) | 16(1) | -1(1) | 1(1) | 2(1) |
| C5 | 24(1) | 37(1) | 20(1) | -2(1) | 6(1) | -9(1) |

| | | | | | | |
|---|---|---|---|---|---|---|
| C10 | 28(1) | 49(2) | 48(2) | -5(1) | 0(1) | -13(1) |

Table 5. Hydrogen coordinates ( x $10^4$) and isotropic displacement parameters ($Å^2$x $10^3$) for **115e**.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H4A | 3278 | 6385 | 2249 | 26 |
| H7A | 3416 | 1667 | 2961 | 23 |
| H6A | 5273 | 2876 | 3923 | 29 |
| H5A | 5236 | 5777 | 3397 | 32 |
| H10A | -506 | 499 | 2495 | 63 |
| H10B | -962 | 1070 | 3678 | 63 |
| H10C | -277 | -624 | 3655 | 63 |
| H1 | 3110(30) | 1870(30) | 5690(30) | 20(8) |

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## BIOGRAPHICAL SKETCH

Ravi Shankar Orugunty was born on March 14, 1970 in Calcutta, India. The son of a Pharmacist/Chemist and was therefore exposed to physical sciences at a very young age. He graduated from Delhi Tamil Higher Secondary School, Lodhi Estate, New Delhi in 1988. He received his Bachelors in Pharmacy in 1992 from Dr. MGR Medical University, Chennai. He obtained his Ph.D in Pharmaceutical Chemistry from the University of Florida in 1998 under the tutelage of Dr. Koppaka. V. Rao. His work during that period involved the isolation of neolignans from *Saururus cernuus.* In order to have a greater understanding of Synthetic organic chemistry and broaden his horizons he decided to do a second Ph.D in organic chemistry under the guidance of Dr. Dennis Wright.